Causal Estimators for Non-Standard Scenarios: Individual Versus Population-Level Causal Effects in Transplantation Treatment Regimes, and Clinical Trials where Compliance is Measured with Error

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Dedication

To those who have given me so much encouragement over the years: my wife, Sarah; my parents, Debbie and Larry; my sister, Lindsey; and my brother, Andy.

Abstract

Inferring and explaining causal relationships is frequently one of the primary goals in public health research. Randomized controlled trials (RCTs) are the gold standard for establishing causal effects, but often RCTs are infeasible or unethical, and we must rely on observational data for inference. Even in the case where RCTs can be conducted causal inference is often difficult due to patient noncompliance. Statistical methods for causal inference are needed in such cases. Although there exist well-established statistical causal inference methods, in this dissertation we develop methods for non-standard scenarios. In Chapter 2, we consider treatment regimes for solid organ transplantation. In Chapters 3 and 4, we consider estimating causal effects in RCTs in the presence of noncompliance. In all cases, we develop novel weighted estimators that are similar to inverse probability of compliance weighted estimators, but the weights are a ratio of probabilities rather than an inverse probability. For solid organ transplantation, these weights are needed so that our estimators have the desired interpretation, and in the case of RCTs in the presence of noncompliance, these weights are needed so that our estimators actually correspond to a causal effect of interest when traditional assumptions about noncompliance are not valid.

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Chapter 1

Introduction

Randomized controlled trials (RCTs) are the gold standard for establishing causation in research with humans (Friedman *and others*, 2015). The randomization seeks to balance both known and unknown participant characteristics that may influence the outcome. Frequently, it is infeasible or unethical to randomize participants to a treatment, intervention, or exposure. In these cases, we often rely on observational data for inference. However, establishing the effect of a treatment with observational data is difficult due to confounding (Greenland *and others*, 1999), that is, when participant characteristics are associated with treatment assignment and with the outcome. An observed difference in the effect of treatments may be due to the treatments themselves, to differences between participant characteristics in the treatment groups, or both.

Even when data from RCTs are available, causal inference is often challenging due to noncompliance, that is, participants not adhering to randomized treatment (Follmann, 2000; Glynn *and others*, 1994). In this scenario, although the assigned treatment is randomized, the treatment actually received is not randomized. Analyzing data for only compliant participants is problematic because compliers may differ systematically from non-compliers, that is, compliance status is confounded (Lee *and others*, 1991).

Statistical methods for causal inference are needed in these cases and when attempting causal inference with observational data. Although the assumptions of the methods are strong and frequently unverifiable, they nevertheless offer means to generate new ideas for research and can be used to plan and conduct future randomized trials.

One popular strategy to address confounding with both observational data and with

noncompliance in RCTs is inverse probability weighting (IPW) (Hernán and Robins, 2006; Robins *and others*, 1994). The technique addresses confounding by modeling treatment assignment as a function of patient characteristics. The model is used to create a weighted "pseudo-population" for statistical inference. If all patient characteristics affecting treatment assignment and the outcome are known and can be correctly modeled, IPW allows for valid causal inference despite confounding in the un-weighted data.

In this dissertation, we develop novel estimators of causal effects in non-standard scenarios. The estimators are similar to and were motivated by IPW estimators, but IPW estimators are insufficient for these scenarios. The weights of my proposed estimators are constructed as ratios of probabilities rather than as an inverses of probabilities.

In Chapter 2, we consider treatment strategies for organ transplantation, specifically whether patients should avoid low-quality organs in the hopes that a better organ may be offered in the future. In transplantation, RCTs are generally impractical, so we must rely on observational registries for inference. To test a particular treatment strategy, we use the outcomes of participants whose treatment history is consistent with a particular treatment strategy, that is, they avoid organs that are low-quality. These patients are said to be "compliant" with a particular treatment strategy. But in the case of solid organ transplantation, cadaveric organs are allocated based on patient condition, and so compliance is confounded. Inverse probability weighted estimators can be used to correct for this confounding and to estimate the anticipated survival for following a treatment strategy, but traditional IPW has an important limitation in this context: the estimated anticipated survival is for a single random patient who adopts the treatment strategy. We show in Chapter 2 that the anticipated survival can be different if the entire population of participants adopts the strategy. We develop a class of estimators to estimate the anticipated survival for either case. The weights are a ratio of the probability of observing a patient's treatment history in the counterfactual world where some portion of patients adopt the strategy, to the probability of observing a patient's treatment history in the observed data.

In Chapter 3, We consider estimating causal effects in clinical trials with noncompliance. Although there exist well-established methods for causal inference in the presence of noncompliance, we argue that investigators frequently assume that compliance is

measured without error. This is frequently an untenable assumption, particularly when compliance is based on participants' self-report. The method was strongly motivated by an RCT testing the efficacy of very low nicotine content cigarettes on cigarettes smoked per day. Although a substantial portion of patients reported strict compliance, that is, reported smoking very low nicotine content cigarettes exclusively, biomarkers of nicotine exposure were inconsistent with this claim for a large portion of patients, indicating that compliance is being reported with error. Because existing causal inference methods assume that compliance is measured without error, a causal estimator without this assumption is needed to estimate causal effects with these data. We argue that in this case compliance should be treated as an unobserved variable, and we propose a novel estimator of the causal effect that weights participants according to the ratio of the probability of compliance given the observed data to the probability of compliance given the confounding variables. Although we treat compliance as an unobserved variable, we show how to estimate the probability of compliance based only on the observed data, resulting in a consistent and asymptotically normal estimator.

In Chapter 4, we develop more general causal estimators for use in clinical trials where compliance is measured with error. Regression-based estimators are one alternative to IPW estimators. Provided that the confounders can be identified, and their effect on the outcome correctly modeled, regression estimators can be used in place of IPW for estimating causal effects. In addition, augmented estimators combine IPW estimators with regression-based estimators. These estimators have the appealing property that if either the regression model or the model for probability of compliance given confounders is correct, the estimators are consistent even if the other model is misspecified. But again, as with IPW estimators, these estimators traditionally have assumed that compliance is measured without error. We propose regression-based estimators, an augmented estimator, and extensions of the weighted estimators presented in Chapter 3 for use in cases where compliance is measured with error.

Chapter 2

Estimating Individual-Level and Population-Level Causal Effects of Organ Transplantation Treatment Regimes

2.1 Chapter 2 Introduction

Determining an optimal rule or regime that dictates when a patient should start treatment is an important step in personalizing medicine (Cain *and others*, 2010). However, determining when a patient should undergo organ transplantation is challenging because the availability and the quality of cadaveric organs on any particular day are random and complex processes.

Because the number of people awaiting all solid organ transplants exceeds the number of available organs in the United States, the United Network for Organ Sharing (UNOS) maintains a national list used to orderly offer available cadaveric organs to potential recipients. For lung transplantation, for example, cadaveric lungs are offered based on the blood type of the donor and recipient, location, and the lung allocation score (LAS), a composite score of over a dozen patient characteristic that quantifies both patients' risk of death on the waiting list and their anticipated survival benefit

from lung transplantation (Egan and Kotloff, 2005). Importantly, although the order in which organs are offered is deterministic, who actually receives the offered organ is random as patients may decline the offer (see Colvin-Adams *and others* (2012) for a description of the lung allocation policy).

Poor quality of the organ is one reason patients may decline an offer. For example, patients transplanted with a lung from donors over age 50 or with a history of smoking generally have poorer post-transplant survival than patients who received lungs from younger, healthier patients (Reyes *and others*, 2010). Although accepting low-quality lungs may lead to poor post-transplant prognosis, declining offered lungs and remaining on the waiting list is not without risk: the LAS system effectively allocates lungs to patients most in need, but it does not guarantee that a patient who declines an organ will be offered another if her condition deteriorates. The challenge is to weigh the potential survival benefit to be gained by forgoing a low-quality organ in favor of waiting for a high-quality organ against the risk that the patient may die before being offered a high-quality organ.

One way to improve a patient's anticipated survival time is to use available observational data to estimate the anticipated survival if the patient were to adopt a particular strategy, or *dynamic treatment regime* (DTR), that dictates which organs should be avoided. Formally, a treatment regime is a function that maps a patient's treatment and covariate history to an action to be taken (Moodie *and others*, 2007). Organ transplantation is an example of a multi-stage treatment regime because each time the patient is offered an organ, she must decide whether to accept it. For lung transplantation, one potential treatment regime for a patient would be "for any viable lung transplantation that is offered, decline the transplantation if the donor was $\geq$ 50 years old or had a history of smoking $\geq$ 20 pack-years, otherwise accept the organ."

Several statistical methods have been proposed to estimate the effect of complying with different DTRs on survival, both within the context of organ transplantation and in other therapeutic areas. The parametric G-formula has been proposed to estimate the counterfactual distribution of various outcomes if patients were to follow a particular DTR by developing a series of models for the waiting list and organ allocation process (e.g., patient arrivals to the waiting list, longitudinal changes in patient

acuity and death while on the waiting list, organ arrivals and their quality, organ allocation, and post-transplant survival. See Robins and Hernán (2008) for a detailed exposition of parametric G-formula). This is the approach used in the Thoracic Simulated Allocation Model used by UNOS to evaluate different allocation policies (see the Thoracic Simulated Allocation Model (TSAM) User's Guide, Scientific Registry of Transplant Recipients, https://www.srtr.org/media/1201/tsam.pdf, accessed April 26, 2017). However, this approach requires developing and correctly specifying a multitude of statistical models to obtain consistent estimators of the counterfactual survival.

Other approaches have sought to avoid modeling the entire waiting list and allocation process. Schaubel *and others* (2006) introduced a sequential stratification method to test whether patients awaiting kidney transplantation should accept kidneys from expanded criteria donors versus remaining on the waiting list and possibly receiving a kidney from a traditional donor in the future. This method can be easily applied to compare the effect of accepting versus declining other marginal organs. However, the approach does not permit direct comparisons of different rules for declining an available organ (e.g., declining all organs from donors over 50 years of age versus declining all organs from donors over 40 years of age). Other methods include inverse probability of compliance weighted (IPCW) Kaplan-Meier and Cox proportional hazards models (Cain and Cole, 2009; Cain *and others*, 2010; Cole and Hernán, 2008; Hernán *and others*, 2006; Hernán and Robins, 2006; Orellana *and others*, 2010). In these methods a patient's follow-up time is considered only while she is "compliant" with a regime of interest. When a patient becomes non-compliant with the regime, her follow-up time is artificially censored. Observations are weighted according to the inverse of probability of compliance to correct for the potential selection bias introduced by the artificial censoring (Hernán *and others*, 2006).

In organ transplantation, the anticipated survival for a given DTR depends on the quality and availability of organs, and these depend on the strategies that other patients follow to accept or decline an organ. This is conceptually similar, although not identical, to the "spillover" (Rubin, 1980) effect described in other contexts. An important limitation in this context of the methods previously developed is that they estimate the anticipated survival if a randomly selected patient were to follow a treatment regime, *and all other patients made no changes to their behavior*. This may be of great interest

to particular patients, but it may have less public health relevance. A policy dictating that certain organs should be avoided would change the dynamics of the waiting list. For example, because patients would decline organs, the size of the waiting list may increase, thus reducing each patients probability of getting a transplant. A meaningful analysis would therefore estimate the causal effect of a treatment strategy on survival *if the entire population of patients were to follow the strategy.*

We demonstrate how we can estimate the causal effect of following a DTR, assuming that all patients are following the DTR of interest, by re-weighting patients based on the probability of following their transplant history in the counterfactual world in which all patients follow the DTR of interest. In Section 2.2, we introduce a potential outcomes framework in which to represent the effect of following a specific regime for accepting or declining an offered organ, and we discuss treatment regimes that we can reasonably estimate using available longitudinal data. In Section 2.3, we introduce a class of IPCW estimators for the anticipated survival distribution if a random patient were to follow a particular regime. The estimator can be used in both the case where no other patients make changes to their behavior and in the case where all patients are following the transplant regime. Section 2.4 discusses a metric of donor organ quality in the context of the proposed estimators. In Section 2.5 we present the results of a simulation study designed to test the small-sample properties of the estimators. Section 2.6 demonstrates our method using data from UNOS, and we conclude in Section 2.7.

2.2 Statistical Framework

To aid the reader, we have included a summary of the notation used throughout the manuscript in Appendix A. In general, uppercase letters represent random variables, while lowercase letters represent realizations of those random variables.

2.2.1 Potential Outcomes

Consider a hypothetical population of patients eligible for organ transplantation. Let $T^*(\infty)$ denote the survival time from listing (i.e., entry on the waiting list) if the patient, possibly contrary to fact, were to never receive a transplanted organ. Define $T^*(b, q)$ as a random patient's counterfactual survival time from listing if the patient were to receive

an organ b days after listing with organ characteristics $q \in \mathcal{Q}$, where $\mathcal{Q}$ is the set of all donor characteristics. Define $X^*(b)$ to be the covariates collected b days after listing for a random patient including whether or not the patient had been previously transplanted and had previously died prior to time b. Throughout, we use the overbar notation to denote history, so that $\overline{X}^*(b)$ is the history of time-dependent covariates through b days after listing. Assume that $X^*(b)$ contains all the information that will be used to accept or decline organs or order patients on the waiting list in any counterfactual scenarios considered below. Because we do not observe $T^*(b,q)$ for all possible b and q, these are known as potential outcomes. Let the set of potential outcomes for the ith patient be $\mathcal{P}_i = \{T_i^*(\infty), T_i^*(b,q), X^*(b) \ \forall \ b \leq T_i^*(\infty), q \in \mathcal{Q})$.

Inferring the distribution of $T^*(b,q)$ is not of primary interest, because there may not be an organ offered to a particular patient b days after listing with characteristics q. Formally, define a transplant regime for whether or not to accept an organ b days after entering the waiting list as a function g which maps from $\overline{X}^*(b)$ and q to an indicator for whether or not the patient should decline an offered organ. We further elaborate of the regimes of interest in Section 2.2.3.

The quality and the availability of organs will vary depending on the rules other patients use to accept or decline organs and the order in which cadaveric organs are offered to potential recipients (i.e., the allocation rules). Therefore, when (or if) a patient receives a transplant while following regime g is random and depends on the regimes other patients use to accept or decline organs. We refer to this as "transplant regime spillover." With this in mind, define $T^*(g,g')$ to be the time a randomly selected patient would have lived if she followed regime g for declining offered organs and all other patients follow regime g'. Note that, in principle, each patient could follow a different regime, but for simplicity we only consider the scenario in which all other patients follow a common regime g'. We make precise what we mean by "all other patients follow regime g'" in Section 2.2.3. Finally, for the purposes of this paper, we assume the allocation rules are the ones currently used and cannot be changed and, therefore, do not index outcomes by the allocation rules used.

The goal of this analysis is to estimate $\Pr\{T^*(g,g') \geq t\}$ for a given $g, g' \in \mathcal{G}$, where $\mathcal{G}$ is the set of all possible treatment regimes. The distribution of $T^*(g,g')$ is a mixture distribution of well-defined counterfactual survival times. If we let $B^{(g,g')}$ and

$Q^{(g,g')}$ be the random time from listing until organ transplantation and vector of organ characteristics for a random subject if she followed regime g for declining offered organs and all other patients follow regime g', then $f_{T^*(g,g')}(t)$, the density of $T^*(g,g')$, is equal to

$$\sum_{\overline{x}(t)} f_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}(t)\right\}\left[\prod_{s=1}^{t} 1-\sum_{q}\rho^{(g,g')}\left\{s,q|\overline{x}(s)\right\}\right] f_{\overline{X}^*(t)}\left\{\overline{x}(t)\right\} \tag{2.1}$$
$$+\sum_{b=1}^{t}\sum_{q}\sum_{\overline{x}(b)} f_{T^*(b,q)|\overline{X}^*(b)}\left\{t|\overline{x}(b)\right\}\left[\prod_{s=1}^{b-1} 1-\sum_{q}\rho^{(g,g')}\left\{s,q|\overline{x}(s)\right\}\right]$$
$$\times\,\rho^{(g,g')}\left\{b,q|\overline{x}(b)\right\} f_{\overline{X}^*(b)}\left\{\overline{x}(b)\right\},$$

where $f_{T^*(b,q)|\overline{X}^*(b)}$ is the conditional density of $T^*(b,q)$ given $\overline{X}^*(b)$, $f_{\overline{X}(t)}$ is the density of time-dependent covariates, and $\rho^{(g,g')}\left\{b,q|\overline{x}(b)\right\}$ is the probability of receiving a transplant b days after listing with organ characteristics q given she is untransplanted $b-1$ days after listing with covariate history $\overline{x}(b)$ and the patient follows regime g while all others follow regime g'. In the preceding, for simplicity of exposition, we have assumed that the organ and patient characteristics are discrete but Equation (2.1) is easily generalized to allow for continuous characteristics.

The derivation of the density of $T^*(g,g')$ given in Equation (2.1) is similar to the density of following a probabilistic dynamic treatment regime given in Murphy *and others* (2001). However, the key difference is that the probability of initiating treatment depends on the treatment regime other patients follow. "Spillover" typically refers to situations in which the distribution of well-defined potential outcomes depends on the treatment assignment of others, which is not the case here. However, we refer to this as transplant regime spillover.

2.2.2 Observed Data

Assume that we observe a cohort of n patients listed for organ transplantation over a period of p days. Let T_i be the observed time from entering the waiting list to death for the ith patient, and X_{ij} be the vector of covariates collected on the ith patient on the jth study day, $j=1,\ldots,p$, including whether or not the subject was eligible (i.e., active on the waiting list) for transplantation. We assume that after transplantation no additional covariate information is collected. For the purposes of this analysis we

will assume that death information and transplant information are recorded daily as they are in the UNOS registry and that the temporal ordering of events on a given day is (1) time-dependent covariates are updated, (2) organs are assigned to patients and are transplanted, and then (3) patients die. Define $N_{ij} = I(L_i + T_i = j)$ and $Y_{ij} = I(L_i + T_i \geq j)$ to be the indicators for whether or not the ith patient died on the jth day of the study and whether the ith patient was at risk for death on the jth day of the study, respectively. In this study, all patients are followed until death or study day p so that N_{ij} and Y_{ij} are observed (i.e., not subject to right-censoring) for all patients for $j = 1, \ldots, p$.

Let S_j be the number of organs available for transplant on the jth day of the study, let Q_{jk} be the characteristics of the kth organ transplanted on the jth day, and let A_{ijk} be the indicator for whether or not the ith person received the kth organ on study day j. Define the filtration

$$E_{ijk} = \left\{ \left(A_{ilm}, Q_{lm}, X_{il}\right)_{l=1,\ldots,j-1; m=1,\ldots,S_l}, X_{ij}, S_j, \left(A_{ijm}, Q_{jm}\right)_{m=1,\ldots,k-1}, Q_{jk}, \right\}.$$

That is, E_{ijk} is the collection of all information on the ith subject at the time of the kth transplant on the jth day but excluding whether the ith patient actually receives the kth organ. Similarly define $E_{\cdot jk}$ to be the collection of information on all subjects $i = 1, \ldots, n$ prior to assigning the kth organ on the jth study day.

Given the data in the observational registry, one can determine the order in which patients were offered the organ. Let R_{ijk} be the rank of the ith patient on the waiting list for the kth organ on the jth day of the study, and assume smaller R_{ijk} indicates higher rank, i.e., $R_{ijk} < R_{i'jk}$ implies that patient i will be offered the kth organ before patient i'. Let $O_{ijk} = \prod_{i':R_{i'jk}<R_{ijk}} 1 - A_{i'jk}$ be the indicator that the ith subject is offered the kth organ on the jth day.

2.2.3 Transplant Regimes

Because transplantation involves many logistical and clinical considerations (e.g. cross-matching, physical examination of the organ anatomy), it is not practical to dictate that a patient/physician must accept an offered organ. For the same reason we do not attempt to infer the distribution of survival times under a regime that dictates when a patient should receive an organ, for example, "receive a transplant the first day LAS

> 50", because an organ may not be available on that particular day. Instead we are interested in transplant regimes that dictate whether or not an available organ should be *declined* based on the organ quality and patient characteristics. We colloquially refer to these organs as "low-quality" organs. Let $D_{ijk}(g, E_{ijk})$ be an indicator for whether or not the kth organ on day j should be avoided by patient i under regime g based on the organ and patient characteristics. To be precise, if the ith patient is "following" or "compliant with" regime g, then the probability of accepting the organ is $\pi_{ijk}^{A(g)}(E_{ijk}) = \pi_{ijk}^{A(\emptyset)}(E_{ijk})\{1 - D_{ijk}(g, E_{ijk})\}$, where $\pi_{ijk}^{A(\emptyset)}(E_{ijk})$ is the probability of accepting the organ if no changes are made to her organ acceptance policy. We will frequently refer to the transplant regime where patients make no changes to their propensity to accept or decline organs, that is, they accept or decline organs with the same probability that they accept or decline organs in the observed data. We refer to this regime as $\emptyset$.

Similarly, let $\pi_{ijk}^{O(g,g')}(E_{\cdot jk})$ denote the conditional probability given the observed data that the ith patient is offered the kth organ on day j given that she is following regime g and all other patients are following regime g'. Note that $\pi_{ijk}^{O(g,g')}(E_{\cdot jk})$ is the probability that all patients who would have ranked higher than the ith decline the organ in the counterfactual world in which they are all following regime g'. Finally, let $\pi_{ijk}^{(g,g')}(a_{ijk}, E_{\cdot jk})$ to be the probability that ith person receives and does not receive if $a_{ijk} = 1$ and $a_{ijk} = 0$, respectively, the kth available organ on the jth day given all the observed information up until the time of assigning that organ, assuming the ith patient is following regime g and all other patients are following regime g'. Note that

$$\begin{aligned}\pi_{ijk}^{(g,g')}(a_{ijk}, E_{\cdot jk}) =& a_{ijk}\pi_{ijk}^{A(g)}(E_{ijk})\pi_{ijk}^{O(g,g')}(E_{\cdot jk}) \\ &+ (1 - a_{ijk})\{1 - \pi_{ijk}^{A(g)}(E_{ijk})\pi_{ijk}^{O(g,g')}(E_{\cdot jk})\}.\end{aligned} \tag{2.2}$$

Similarly, define $\overline{\pi}_{ij}^{(g,g')}(\overline{a}_{ij}, \overline{E}_{\cdot jS_j}) = \prod_{m=1}^{j}\prod_{k=1}^{S_m}\pi_{imk}^{(g,g')}(a_{imk}, E_{\cdot mk})$, the probability that the ith patient has her treatment history through study day j given that she is following regime g and all other patients follow regime g'.

2.2.4 Identifying Assumptions

To estimate the causal effect of a treatment regime on the survival probability t days after entering the waiting list, we must make the following assumptions to relate the

observed data to the distribution of the potential outcomes (Robins and Hernán, 2008).

We assume that $1-\pi_{ijk}^{A(g)}(E_{\cdot jk}) > 0 \; \forall i, j, k$. That is, there is some non-zero probability that a patient will remain compliant with a particular regime g of the form discussed in Section 2.2.3. This is known as the *positivity* assumption.

We make the so-called *sequential ignorability* or *no unmeasured confounders* assumption that the probability of receiving an organ at any time depends only on the observed data up until that time and not additionally on any potential outcomes. This assumption implies A_{ijk} is conditionally independent of $\mathcal{P}$ given $E_{\cdot jk} \; \forall \; i = 1, ..., n, \; j = 1, ..., p,$ and $k = 1, \ldots, S_j$, where $\mathcal{P} = (\mathcal{P}_1, \ldots, \mathcal{P}_n)$.

We assume that $T_i = T_i^*(t, q)$ if $\sum_{k=1}^{S_j} A_{i,L_i+t,k} = 1$ and $\sum_{k=1}^{S_j} A_{i,L_i+t,k} Q_{L_i+t,k} = q$, and similarly $T_i = T_i^*(\infty)$ if $\sum_{m=1}^{j} \sum_{k=1}^{S_m} A_{imk} = 0$. This assumption is referred to as the *consistency* assumption.

Finally, we assume that the availability and the characteristics of cadaveric organs and when patients enter the waiting list does not depend on the characteristics of the patients on the waiting list or the regimes that patients use to accept or decline organs. We refer to this as the waiting list stability assumption.

2.3 Class of Estimators

To estimate $S_r(g, g')$, the survival probability r days after entering the waiting list for a random patient who follows regime g while all other patients follow regime g', we first estimate $\lambda_t(g, g')$, the discrete-time hazard of death t days after entering the waiting list, $t = 1, \ldots, r$, for a randomly selected patient if she were to following regime g and all other patients followed regime g'. Assuming for now that $\overline{\pi}_{ij}^{(\emptyset,\emptyset)}(\overline{A}_{ij}, \overline{E}_{\cdot jS_j})$ and $\overline{\pi}_{ij}^{(g,g')}(\overline{A}_{ij}, \overline{E}_{\cdot jS_j})$ are known, we can estimate $\lambda_t(g, g')$ by solving the estimating equation

$$\sum_{j=1}^{p} \sum_{i=1}^{n} \frac{\overline{\pi}_{ij}^{(g,g')}(\overline{A}_{ij}, \overline{E}_{\cdot jS_j})}{\overline{\pi}_{ij}^{(\emptyset,\emptyset)}(\overline{A}_{ij}, \overline{E}_{\cdot jS_j})} \left\{ N_{ij} - Y_{ij} \lambda_t(g, g') \right\} I(j - L_i = t) = 0. \tag{2.3}$$

The vector of estimated discrete-time hazards $\hat{\lambda}(g, g') = \left\{ \hat{\lambda}_1(g, g'), \ldots, \hat{\lambda}_r(g, g') \right\}^T$ is the solution to the corresponding r-dimensional estimating equation. The survival probability $S_r(g, g')$ can easily be estimated as $\hat{S}_r(g, g') = \prod_{t \leq r} \left\{ 1 - \hat{\lambda}_t(g, g') \right\}$, which

is equivalent to a weighted Kaplan-Meier survival estimator. Note that the IPCWs $\frac{\overline{\pi}_{ij}^{(g,g')}(\overline{A}_{ij},\overline{E}_{\cdot jS_j})}{\overline{\pi}_{ij}^{(\emptyset,\emptyset)}(\overline{A}_{ij},\overline{E}_{\cdot jS_j})}$ are a ratio of the probability of observing the transplant history under regime g while all others follow regime g' to the probability of the observed treatment history for the ith patient.

Under the assumptions in Section 2.2.4, the left-hand side of equation (2.3) is a mean-zero estimating function. For notational simplicity, define $A_{\cdot jk} = \{A_{1jk}, \ldots, A_{njk}\}$ and similarly for other random variables, $A_{-ijk} = \{A_{1jk}, \ldots, A_{i-1,jk}, A_{i+1,jk}, A_{njk}\}$, and $E_{ij0} = \{E_{i,j-1,S_{j-1}}, A_{i,j-1,S_{j-1}}\}$. Let f denote the conditional mass function of T_i given $E_{\cdot L_i+t+1,0}$; g the conditional mass function of A_{-ijk} given $E_{\cdot jk}, A_{ijk}$; h the conditional mass function of Q_{jk} given $E_{\cdot j0}, X_{\cdot j}, S_j$; u the conditional density of S_j given $E_{\cdot j0}, X_{\cdot j}$; v the conditional density of $X_{\cdot j}$ given $E_{\cdot j0}$; and w denote the mass function of L_i. Finally, define h_i and u_i as above but conditioning on E_{ijk} and X_{ij} rather than $E_{\cdot jk}$ and $X_{\cdot j}$. Uppercase letters with overbars will be used to denote the corresponding survival functions.

To show this that the estimating function has expectation zero, we begin by writing the expectation of the estimating function for the ith patient as the sum of the estimating function with respect to the observed data density.

$$
\begin{aligned}
& E\left[\frac{\prod_{j=L_i}^{L_i+t}\prod_{k=1}^{S_j}\pi_{ijk}^{(g,g')}(A_{ijk},E_{\cdot jk})}{\prod_{j=L_i}^{L_i+t}\prod_{k=1}^{S_j}\pi_{ijk}^{(\emptyset,\emptyset)}(A_{ijk},E_{\cdot jk})}\left\{I(T_i=t)-I(T_i\geq t)\lambda_t(g,g')\right\}\right] \\
&= \sum\cdots\sum\frac{\prod_{j=L_i}^{L_i+t}\prod_{k=1}^{S_j}\pi_{ijk}^{(g,g')}(a_{ijk},E_{\cdot jk})}{\prod_{j=L_i}^{L_i+t}\prod_{k=1}^{S_j}\pi_{ijk}^{(\emptyset,\emptyset)}(a_{ijk},E_{\cdot jk})}\left\{I(T_i=t)-I(T_i\geq t)\lambda_t(g,g')\right\}f(t_i|e_{\cdot l_1+t+1,0}) \\
&\quad\times\prod_{j=l_i}^{l_i+t}\left[v(x_{\cdot j}|e_{\cdot j0})u(s_j|e_{\cdot j0},x_{\cdot j})\left\{\prod_{k=1}^{S_j}h(q_{jk}|e_{\cdot j0},x_{\cdot j},s_j)\pi_{ijk}^{(\emptyset,\emptyset)}(a_{ijk},e_{\cdot jk})g(a_{-ijk}|e_{\cdot jk},a_{ijk})\right\}\right]w(l_i) \\
&= \sum\cdots\sum\left\{f(t|e_{\cdot l_1+t+1,0})-\overline{F}(t|e_{\cdot l_1+t+1,0})\lambda_t(g,g')\right\} \\
&\quad\times\prod_{j=l_i}^{l_i+t}\left[v(x_{\cdot j}|e_{\cdot j0})u(s_j|e_{\cdot j0},x_{\cdot j})\left\{\prod_{k=1}^{S_j}h(q_{jk}|e_{\cdot j0},x_{\cdot j},s_j)\pi_{ijk}^{(g,g')}(a_{ijk},e_{\cdot jk})g(a_{-ijk}|e_{\cdot jk},a_{ijk})\right\}\right]w(l_i) \\
&= \sum\cdots\sum\left(\left[f_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}_{i,l_i+t}\right\}-\overline{F}_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}_{i,l_i+t}\right\}\lambda_t(g,g')\right]f_{\overline{X}^*(t)}\left\{\overline{x}_{i,l_i+t}\right\}\left\{1-\sum_{j=1}^{l_1+t}\sum_{k=1}^{s_j}a_{ijk}\right\}\right. \\
&\quad\left.+\sum_{b,q}\left[f_{T^*(b,q)|\overline{X}^*(b)}\left\{t|\overline{x}_{i,l_i+b}\right\}-\overline{F}_{T^*(b,q)|\overline{X}^*(b)}\left\{t|\overline{x}_{i,l_i+b}\right\}\right]\lambda_t(g,g')\left]f_{\overline{X}^*(b)}\left\{\overline{x}_{i,l_i+b}\right\}\left\{\sum_{k=1}^{s_{l_i+b}}a_{i,l_i+b,k}I(q_{l_i+b,k}=q)\right\}\right)\right. \\
&\quad\times\prod_{j=l_i}^{l_i+t}\left[u_i(s_j|e_{ij0},x_{ij})\left\{\prod_{k=1}^{S_j}h_i(q_{jk}|e_{ij0},x_{ij},s_j)\pi_{ijk}^{(g,g')}(a_{ijk},e_{ijk})\right\}\right]w(l_i)
\end{aligned}
$$

$$
\begin{aligned}
=&\sum_{\overline{x}(t)}\left[f_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}(t)\right\}-\overline{F}_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}_{i,l_i+t}\right\}\lambda_t(g,g')\right]\left[\prod_{s=1}^{t}1-\sum_q\rho^{(g,g')}\left\{s,q|\overline{x}(s)\right\}\right]f_{\overline{X}^*(t)}\left\{\overline{x}(t)\right\}\\
&+\sum_{b=1}^{t}\sum_q\sum_{\overline{x}(b)}\left[f_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}(b)\right\}-\overline{F}_{T^*(\infty)|\overline{X}^*(t)}\left\{t|\overline{x}_{i,l_i+t}\right\}\lambda_t(g,g')\right]\\
&\times\left[\prod_{s=1}^{b-1}1-\sum_q\rho^{(g,g')}\left\{s,q|\overline{x}(s)\right\}\right]\rho^{(g,g')}\left\{b,q|\overline{x}(b)\right\}f_{\overline{X}^*(b)}\left\{\overline{x}(b)\right\}\\
=&0,
\end{aligned}
$$

where the third equality follows from assuming that $\mathcal{P}_i$ is independent of $\mathcal{P}_{i'}$ and that under the consistency, ignorability, and waiting list stability assumptions, the distribution of T_i given $E_{\cdot l_i+t+1,0}, A_{i,l_i+b,k}=1, Q_{l_i,k}=q$ is equal to the distribution $T_i^*(b,q)$ given $\overline{X}_i^*(b)$. The fourth equality follow from the fact that under the identifying assumptions in Section 2.2.4,

$$
\begin{aligned}
&\sum_{s_j}\sum_{q_{jk}}\left\{\sum_{k=1}^{s_{l_i+b}}a_{i,l_i+b,k}I(q_{l_i+b,k}=q)\right\}\prod_{j=l_i}^{l_i+t}\left[u_i(s_j|e_{ij0},x_{ij})\left\{\prod_{k=1}^{S_j}h_i(q_{jk}|e_{ij0},x_{ij},s_j)\pi_{ijk}^{(g,g')}(a_{ijk},e_{ijk})\right\}\right]w(l_i)\\
&=\left[\prod_{s=1}^{b-1}1-\sum_q\rho^{(g,g')}\left\{s,q|\overline{x}(s)\right\}\right]\rho^{(g,g')}\left\{b,q|\overline{x}(b)\right\},
\end{aligned}
$$

where we have used the fact that $A_{ijk}=1$ implies that $A_{ij'k'}=0$ if $j\neq j'$ or $k\neq k'$.

We have implicitly argued that the estimating function is not the sum of independent observations, because individuals' actions on the waiting list impact others. However, one can show that covariance between subjects who are on the waiting list at separate times is 0. Therefore, if we are willing to assume that the waiting list "turns over" after m individuals (a reasonable assumption for this acutely ill population), then under standard regularity conditions for

m-dependent processes (DasGupta, 2008), $\hat{\lambda}(g, g')$ is a consistent and asymptotically normal estimator for $\lambda(g, g')$ as $n \to \infty$.

2.3.1 Estimating the Denominator of the Inverse Probability Weights

In most applications, the numerator and denominator of the weights are unknown and must be estimated. We discussed in Section 2.2.3 that the probability a particular patient is offered an organ depends on the probability that all others who rank higher on the waiting list decline the organ. The denominator of the weights, however, is just the probability of observed treatment history assuming all patients follow regime $\emptyset$ (the regime in which all patients make no change in their propensity to accept or decline organs). To estimate this probability, we only require a model for the probability that patients accept organs given that they are offered based on the observed data. Although many models are possible, a natural model for accepting an organ given that is organ is offered is the logistic model

$$\pi_{ijk}^{A(\emptyset)}\left(E_{ijk};\varphi\right)=\left\{1+e^{-\left(\varphi_0+\varphi_1^T\overline{X}_{ij}+\varphi_2^T\overline{X}_{ij}Q_{jk}+\varphi_3^TQ_{jk}\right)}\right\}^{-1}, \tag{2.4}$$

where $\overline{X}_{ij}Q_{jk}$ is a vector of donor-patient interaction characteristics. These regression parameters can be easily estimated by solving the estimating equation

$$\sum_{i=1}^{n}\sum_{j=1}^{p}\sum_{k=1}^{S_j}O_{ijk}\left[\frac{A_{ijk}-\pi_{ijk}^{A(\emptyset)}(E_{ijk})}{\pi_{ijk}^{A(\emptyset)}(E_{ijk})\left\{1-\pi_{ijk}^{A(\emptyset)}(E_{ijk})\right\}}\right]\frac{\partial\pi_{ijk}^{A(\emptyset)}(E_{ijk})}{\partial(\varphi_0,\varphi_1^T,\varphi_2^T,\varphi_3^T)^T}=0. \tag{2.5}$$

The estimated coefficient vector $\hat{\varphi}=(\hat{\varphi_0},\hat{\varphi_1}^T,\hat{\varphi_2}^T,\hat{\varphi_3}^T)^T$ can now be used to estimate $\pi_{ijk}^{A(g)}(E_{ijk};\varphi)$ and $\pi_{ijk}^{O(\emptyset,\emptyset)}(E_{\cdot jk};\varphi)=\prod_{i:R_{i'jk}<R_{ijk}}\{(1-\pi_{i'jk}^{A(\emptyset)}(E_{i'jk};\varphi)$ in Equation (2.2) to estimate the denominator of the weights in Equation (2.3), i.e., $\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij},\overline{E}_{\cdot jS_j}\right)$.

2.3.2 Estimating the Numerator of the Inverse Probability Weights

To estimate $S_r(g,\emptyset)$, estimating the numerator of the weights is straightforward. In this case,

$$\begin{aligned}\pi_{ijk}^{(g,\emptyset)}(a_{ijk},E_{jk})=&a_{ijk}\pi_{ijk}^{A(g)}(E_{ijk})\pi_{ijk}^{O(g,\emptyset)}(E_{\cdot jk})\\&+(1-a_{ijk})\left\{1-\pi_{ijk}^{A(g)}(E_{ijk})\pi_{ijk}^{O(g,\emptyset)}(E_{\cdot jk})\right\}.\end{aligned}$$

Although we wrote $\pi_{ijk}^{O(g,\emptyset)}$ for consistent notation, note that if subject i is compliant with regime g through study day j, then $\pi_{ijk}^{O(g,\emptyset)}(E_{\cdot jk})=\pi_{ijk}^{O(\emptyset,\emptyset)}(E_{\cdot jk})$ (the conditional probability of being offered an organ depends on the actions of other patients, all of

whom are following regime $\emptyset$) which can be is easily estimated as described above. Similarly, $\hat{\pi}_{ijk}^{A(g)}(E_{ijk}) = \pi_{ijk}^{A(\emptyset)}\left(E_{ijk};\hat{\varphi}\right)\left\{1 - D_{ijk}\left(g, E_{ijk}\right)\right\}$.

When $g' \neq \emptyset$, estimating the numerator of the weights is more challenging. Although estimating $\pi_{ijk}^{A(g)}$ using Model 2.4 is straightforward, if all patients are following regime g', we can no longer use $\prod_{i:R_{i'jk}<R_{ijk}}\{(1 - \pi_{i'jk}^{A(g')}(E_{i'jk};\hat{\rho})\}$, to estimate the probability of being offered an organ because the number of patients on the waiting list and their characteristics at the time the organ is offered would be different than in the observed data. That is, in the counterfactual world in which patients follow regime g' the order for offering an available organ would be different from the rank, R_{ijk}, in the observed data.

Note that $\pi_{ijk}^{O(g,g')}(E_{\cdot jk}) = E\{\pi_{ijk}^{O(g,g')}(E_{\cdot jk}^{(g,g')}, E_{\cdot jk})|E_{\cdot jk}\} = E\{\pi_{ijk}^{O(g,g')}(E_{\cdot jk}^{(g,g')})|E_{\cdot jk}\}$, where $E_{\cdot jk}^{(g,g')}$ is the data we would have observed up to the allocation of the kth organ on the jth day had all patients followed regime g' and the ith patient followed regime g and $\pi_{ijk}^{O(g,g')}(E_{\cdot jk}^{(g,g')})$ is the probability the ith subject is offered the kth organ on the jth day given the counterfactual data. Note that given $E_{\cdot jk}^{(g,g')}$ calculation of the probability of being offered an organ is straightforward and would follow a similar approach to that outlined for the observed data.

However, analytically evaluating the outer expectation is challenging. Therefore, we propose to estimate this quantity using Monte Carlo integration/summation. To do so, we must be able to simulate $E_{\cdot jk}^{(g,g')}$ given the observed data $E_{\cdot jk}$. We describe how one can simulate such a hypothetical dataset with minimal assumptions.

Given $E_{\cdot jk}$, patient and organ arrival times and their characteristics are fixed. To allocate organs, we assume that if in the observed data $O_{ijk} = 0$ (i.e., we do not know whether or not the ith subject would have accepted the kth organ on the jth day) patients accept offered organs in the hypothetical dataset with probability $\left\{1 - D_{ijk}(g, E_{ijk}^{(g,g')})\right\}\pi_{ijk}^{A(\emptyset)}(E_{ijk}^{(g,g')})$ for the ith subject and with probability $\left\{1 - D_{ijk}(g', E_{ijk}^{(g,g')})\right\}\pi_{ijk}^{A(\emptyset)}(E_{ijk}^{(g,g')})$ for all others. If in the observed data the patient was offered the organ, then in the hypothetical dataset the patient accepts the organ with probability 1 if $A_{ijk} = 1$ and with probability 0 if $A_{ijk} = 0$ (i.e., if in the observed data we know a patient accepted or declined an organ than this is preserved in the simulated dataset).

Similarly, because we condition on $E_{\cdot jk}$, patients in the simulated dataset begin with

the same covariate trajectory as in the observed dataset. However, it is possible for a subject in the observed dataset to remain on the waiting list in the simulated dataset longer than in the observed one. In such a case, we need to simulate their covariate trajectory until death or transplant. Rather than postulate a parametric model for X_{ij} given $\overline{X}_{ij'}, \overline{A}_{ij'S_{j'}} = 0$ (for $j' < j$), we use hot deck imputation. When discussing the imputation, we avoid the "donor-recipient" verbiage common in the literature (for example, see Andridge and Little (2010)), because that can obviously create confusion here. We refer to an individual whose values are to be filled in as the "borrower" and the pool of potential patients whose values could be used as the "lenders."

If the ith patient was transplanted on the jth day in the observed data, the data for the eligible lenders is the set

$$\left[\left\{X_{i'j'}, X_{i'(j'+1)}, \cdots\right\}, \left\{(A_{i'j'k})_{k=1,\cdots,S_{j'}}, (A_{i'(j'+1),k})_{k=1,\cdots,S_{(j'+1)}}, \cdots\right\}, T_{i'}\right]_{i' \neq i}$$

such that $j - L_i = j' - L_{i'}$, that is, the potential data are the covariate history, transplantation history, and death time for each lender, taken from the time where the lender had been on the waiting list for as long as the borrower, but not necessarily concurrently. The lender can be selected as the patient whose $X_{i'}$ minimizes $|X_{ij} - X_{i'j'}|$ or some other distance metric for multi-dimensional covariates (including past history of patient covariates). The borrower's information from time j is replaced by the lender's data beginning at time j'. If the lender received a transplant, the process may be repeated.

Typically, in Monte Carlo interegration one would simulate several datasets and average the integrand across them to estimate $\pi_{ijk}^{O(g,g')}(E_{\cdot jk})$. However, in this application, simulating such a dataset can be computationally intensive when combined with resampling methods for standard error estimation, and we have found that simulating a single dataset to estimate $\pi_{ijk}^{O(g,g')}(E_{\cdot jk})$ for all i, j, and k is sufficient. Note that to estimate $\pi_{ijk}^{O(g,g')}(E_{\cdot jk})$ we do not need to simulate post-transplant outcomes.

Because estimating the numerator of the weights is a complicated function of the observed data, we recommend estimating the standard error of $\hat{S}_r(g, g')$ using the nonparametric bootstrap (Efron, 1979).

2.4 Defining Lower Quality Organs

In some applications the definition of a "low-quality" organ may be defined *a priori*. For example, we may define an organ as low-quality if the donors has smoked more than 20 pack-years. Here, however, we consider treatment regimes of the type "decline all organs in the lowest d percentile of donor quality." In this scenario we define "low-quality" as a continuous measure depending on donor and donor-recipient interaction characteristics, and we estimate those combinations of characteristics that lead to poorer survival. We can then estimate the anticipated survival if a patient were to avoid organs below a certain threshold of the donor quality score. We assume that, given $\overline{X}^*(b)$, the distribution of $T^*(b,q) - b$ (the potential residual lifetime after transplantation) follows a discrete-time proportional hazards model. That is,

$$\Pr\left\{T^*(b,q) - b = t\right\} = \lambda_t^{PT} \exp\left\{\xi_1^T \overline{X}^*(b) + \xi_2^T Q + \xi_3^T \overline{X}^*(b) Q\right\},$$

where λ_t^{PT} is the baseline post-transplantation discrete-time hazard of death t days after transplantation. We can estimate $\xi = \left(\xi_1^T, \xi_2^T, \xi_3^T\right)^T$ using the observed data. For an organ with characteristics q and a potential recipient with characteristics $\overline{X}^*(b)$, we define the organ quality score as $-\left\{\xi_2^T Q + \xi_3^T \overline{X}^*(b) Q\right\}$. We may now define a low-quality organ as one that is below a threshold h, that is

$$D_{ijk}(g, E_{ijk}) = I\left[-\left\{\xi_2^T Q + \xi_3^T \overline{X}^*(j - L_i) Q\right\} < h\right].$$

For example, because we assume that each organ is of different quality for each patient due to patient-donor interaction characteristics, we can define the collection of potential donor scores for the ith participant as
$\mathcal{Q}_i = \left(\left[-\left\{\xi_2^T Q_{jk} + \xi_3^T \overline{X}^*(j - L_i) Q_{jk}\right\}\right]_{j=1,\ldots,p, k=1,\ldots,S_j}\right)$. The threshold h_i for the ith patient can be defined as a quantile of $\mathcal{Q}_i$.

2.5 Simulation Study

We designed a simulation study to test the small-sample performance of the proposed estimators. The `R` code for the simulation is available at `https://github.com/jeffrey-boatman/transplant_simulation`. Patient entered the waiting list and organs arrived according to independent Poisson processes with rate parameters 0.5 and

0.32, respectively. Participants were assigned a time-dependent covariate X_{ij} representing disease severity, with higher scores indicating a greater hazard of death on the waiting list and a greater need for transplantation. For each subject we generated $b_{i0} \sim N(-1, 1)$ and $b_{i1} \sim N\left(\frac{1}{365}, \frac{1}{(4 \cdot 365)^2}\right)$. For study day j and a subject who arrived to the waiting list on day L_i, we let $X_{ij} = b_{i0} + b_{i1} \cdot \lfloor \frac{j - L_i}{30} \rfloor \cdot 30$, where $\lfloor \cdot \rfloor$ is the floor function, so that covariate values were updated every 30 days. Patients and organs were randomly assigned an ABO blood-type based on the probability observed in the analysis in Section 2.6. Each organ was assigned a binary indicator variable for "low-quality" with probability 0.5. For each organ arrival on study day j, the waiting list ranking was based on patient-donor blood-type match (exact match and then compatible) and then by the X_{ij} value similar to the ordering for cadaveric lungs. Patients accepted the organ with probability $\left\{1 + e^{\left(-\varphi_0 - x_{ij}^T \varphi_1\right)}\right\}^{-1}$ with $\varphi_0 = -2.5$ and $\varphi_1 = 0.25$. In the results reported here, we analyzed data collected over a 10 year observational period during which the waiting list had reached a steady state. Specifically, we considered the first 10,000 days of each simulated dataset as a burn-in period (i.e., a period of time while the waiting list stabilized analogous to the early years of cadaveric transplantation) and used information collected over the following 10 years in the analysis.

We estimated the survival distribution assuming a randomly selected patient follows the treatment regime $g =$ *decline all low-quality organs* while (a) all other subjects followed their current propensity to accept or decline an offered organ (followed regime $\emptyset$), or (b) all other subjects follow regime g. In addition to the IPCW estimators proposed in Section 2.3 to estimate $S_t(g, \emptyset)$ and $S_t(g, g)$ we considered an ad hoc estimator, $\hat{S}_t(NC)$, that censors individuals at the time of non-compliance from the regime g but does not use any weights. This is not a consistent estimator for any causal effect of interest; we include this ad hoc estimator as it is used commonly in practice. For each estimator we report results for 1,000 Monte Carlo data sets. We estimated the standard error of the estimators using 100 bootstrap re-sampled data sets.

$S_t(g, \emptyset)$ and $S_t(g, g)$, the true survival probabilities t days after entering the waiting list for following regime g, are not available in closed form. Therefore, the survival curves were estimated via Monte Carlo simulation. To estimate $S_t(g, \emptyset)$, for each simulated data set we randomly selected one observation and forced it to decline all low-quality organs, whereas high-quality organs were accepted with probability $\left\{1 + e^{\left(-\varphi_0 - x_{ij}^T \varphi_1\right)}\right\}^{-1}$.

Similarly, to estimate $S_t(g, g)$, for each Monte Carlo dataset we forced all individuals to decline all low-quality organs. The Monte Carlo data sets were independent of the ones to evaluate the proposed estimators.

Table 2.1 shows the true survival probabilities, the bias of the estimators, and coverage probabilities of 95% Wald-type confidence intervals for 4 time points. Although $\hat{S}_t(NC)$ is a convenient and frequently used estimator, it does not consistently estimate any causal effect of interest, and the bias is large for all time points for both causal estimands. For all time points, $S_t(g, \emptyset)$ is greater than $S_t(g, g)$, indicating that in this example, the causal estimand varies based on the question of interest. Importantly, $\hat{S}_t(g, \emptyset)$ and $\hat{S}_t(g, g)$ are not interchangeable: the mean of each estimator is close to its target, but $\hat{S}_t(g, \emptyset)$ is a substantially biased estimator for $S_t(g, g)$, and $\hat{S}_t(g, g)$ is a substantially biased estimator for $S_t(g, \emptyset)$. The simulation results demonstrate the good performance of the estimators, but, perhaps more importantly, they highlight the danger of a naive analysis that fails to carefully specify the target of estimation: an analyst attempting to estimate $S_t(g, g)$ by using the more common estimator $\hat{S}_t(g, \emptyset)$ may draw erroneous conclusions.

2.6 Application to UNOS Data

We illustrate our method with data from the UNOS national registry of lung transplants and use the continuous measure of lung quality described in Section 2.4. The observational period included transplants between May 4, 2005 and Sept 30, 2011.

We estimated ξ, the coefficients for the lung quality model, following the approach in Section 2.4. To be eligible for inclusion in the analysis of the lung quality score, patients must have been older than 18, not received a previous lung transplant, and not listed for simultaneous heart transplant. A total of $n_o = 9,091$ patients contributed to the lung quality model. With these patients we modeled post-transplant survival with recipient, donor, and recipient-donor interaction characteristics as predictors. These included recipient age, donor age, LAS at time of transplant (LAS-T), an indicator for donor history of diabetes, patient native disease group, transplant type, an indicator for patient being on life support at time of transplant, donor race, donor-patient height difference, and recipient body mass index. Restricted cubic spline basis functions with

Table 2.1: Chapter 2 Simulation Results

			Estimator Bias			CP	
Target	t	True Survival	$\hat{S}(NC)$	$\hat{S}(g,\emptyset)$	$\hat{S}(g,g)$	$\hat{S}(g,\emptyset)$	$\hat{S}(g,g)$
$S_t(g,\emptyset)$	180	0.785	0.010	-0.006	-0.018	0.954	0.735
	360	0.636	0.029	-0.000	-0.036	0.966	0.519
	540	0.533	0.039	0.003	-0.056	0.954	0.269
	720	0.463	0.045	0.004	-0.073	0.951	0.152
$S_t(g,g)$	180	0.770	0.024	0.009	-0.003	0.882	0.967
	360	0.599	0.066	0.037	0.001	0.333	0.978
	540	0.471	0.101	0.065	0.006	0.045	0.972
	720	0.382	0.125	0.084	0.007	0.014	0.960

Bias and Coverage Probabilities (CP) of 95% CIs from simulation. $S_t(g,\emptyset)$ and $S_t(g,\emptyset)$ are the simulated true survival probabilities t days after entering the waiting list for following regime g assuming either no other patients follow g or all other patients follow g, respectively. Their estimators are $\hat{S}_t(g,\emptyset)$ and $\hat{S}_t(g,\emptyset)$. $\hat{S}(NC)$ is a naive estimator that censors patients at non-compliance, but does not use weights.

4 knot points were used for continuous covariates to model nonlinear associations with the log hazard. Estimated coefficients from the model are shown Appendix A.

To compare treatment regimes based on donor quality, inclusion criteria were the same as above except that we now included both transplanted and non-transplanted patients. The total number of patients was $n_p = 13,039$. As predictors in the logistic regression model for the probability of accepting we included patient age, current LAS, time on the waiting list, native disease, patient-donor height difference, an indicator for donor smoking ≥ 20 pack-years, and an indicator for donor age ≥ 50 and its interaction with the patient age. As before, we used restricted cubic splines to allow for a nonlinear associated with the log odds of accepting a donor organ. Estimated coefficients from the model are shown in Appendix A. We created the simulated data set used in estimating the numerator of the IPCWs as described in Section 2.3.2. For the ith patient transplanted on the jth day, the lender i' was selected as $\arg\min_{i'} \left(|LAS_{ij} - LAS_{i'j'}| : j - L_i = j' - L_{i'}\right)$. If patient i' later received a transplant,

the process was repeated until the ith patient's LAS trajectory was imputed through time of death with no transplantation. Because LAS was the only time-varying covariate considered in the organ acceptance model, no other variables aside from LAS were imputed.

We considered treatment regimes of the form "decline all donor organs below the qth percentile of donor quality scores if LAS is below M; if LAS $\geq M$, any donor organ is acceptable", where q and M can vary. LAS ranges from 0 to 100 (median LAS-T 38.79; 25th and 75th percentiles: 34.23, 47.27) with greater score indicating greater patient acuity and anticipated benefit for transplant. Examining these regimes allows us to investigate the effect of avoiding low quality organs while the patient is less acute. Importantly, we considered scenarios in which a single patient adopted the treatment regimes as well as all patients on the waiting list to investigate the effect of "transplant regime spillover." Note that under regimes of the this form, patients are never considered non-compliant for declining organs, they are only ever considered non-compliant for accepting organs that violate the treatment regime. Because we assumed that the organ would be of variable quality for each patient due to patient-donor interaction characteristics, we estimated the organ quality for each potential recipient for each possible donor in the dataset, and the distribution of these scores was used to define the qth percentile for each patient.

We selected 4 scenarios to illustrate the proposed estimators. In each case we compare the estimates to the estimated survival if no subjects were to alter their propensity to accept an organ using the Kaplan-Meier estimator where all patients have a weight of 1. The results are shown in Figure 2.1 and in Table 2.2, with standard errors estimated using the bootstrap. In plot (a), we illustrate that the anticipated survival for a random patient following the treatment regime "decline all organs when the LAS is less than 40" is different depending on whether all patients follow the regime or only the single individual does. In both cases, the anticipated survival is better than in the observed data, but the benefit is increased if all patients follow the regime rather than if only a single individual does. In particular, compared to the unweighted Kaplan-Meier survival estimate, the 2-year cumulative percentage(SE) died is lower by 6.4(1.93) if all patients follow the regime and by 2.0(1.31) for a single patient who follows the regime; the 3-year cumulative percentage(SE) died is lower by 3.7(2.11) if all patients follow the

regime and by 1.8(1.31) for a single patient who follows the regime. The benefit for a single random patient who adopts the regime only comes from avoiding transplantation, a procedure with significant peri-operative mortality while the patient is less acute. But if all patients adopt the regime, this prevents relatively healthy patients (ones who are unlikely to die soon on the waiting list) from receiving cadaveric organs and ensures that more organs are available for the most acute patients.

Plot (b) shows the anticipated survival when all patients follow the regime with q fixed at 100 (i.e., regimes in which patients declined all organs) and M varying from 35 to 50 in increments of 5. At lower values of M, there is an anticipated survival benefit. That is, for patients with less acuity would benefit from delaying organ transplant until their LAS increases, a finding consistent with previous research which found no anticipated survival benefit for those transplanted at low LAS (Vock *and others*, 2017, 2013). However, as M increases above 40, the anticipated survival declines, and eventually the risk of death exceeds the observed survival.

Plots (c) and (d) demonstrate that the effect of an organ quality threshold depends on the LAS threshold M. Plot (c) shows that for M at 35, as q increases (i.e., declining a greater number of organs) the survival continues to increase. That is, patients with relatively low LAS are best served by avoiding all organ transplants, even with high-quality organs. In plot (d) we consider the same scenario but with $M = 50$. Here there is a modest survival benefit until $q = 100$, at which point the anticipated survival is worse than in the observed data. Here it appears that patient with high LAS scores may gain a modest survival benefit by declining the worst organs, but declining all organs has a negative impact on survival. The small difference in expected survival among different regimes with different organ quality thresholds is consistent with previous work demonstrating the poor predictive ability of many donor factors on post-transplant survival (Chaney *and others*, 2014; Reyes *and others*, 2010).

2.7 Chapter 2 Discussion

We have demonstrated how we can approach the problem of testing treatment regimes when treatment is available stochastically and when the effect of the treatment regime

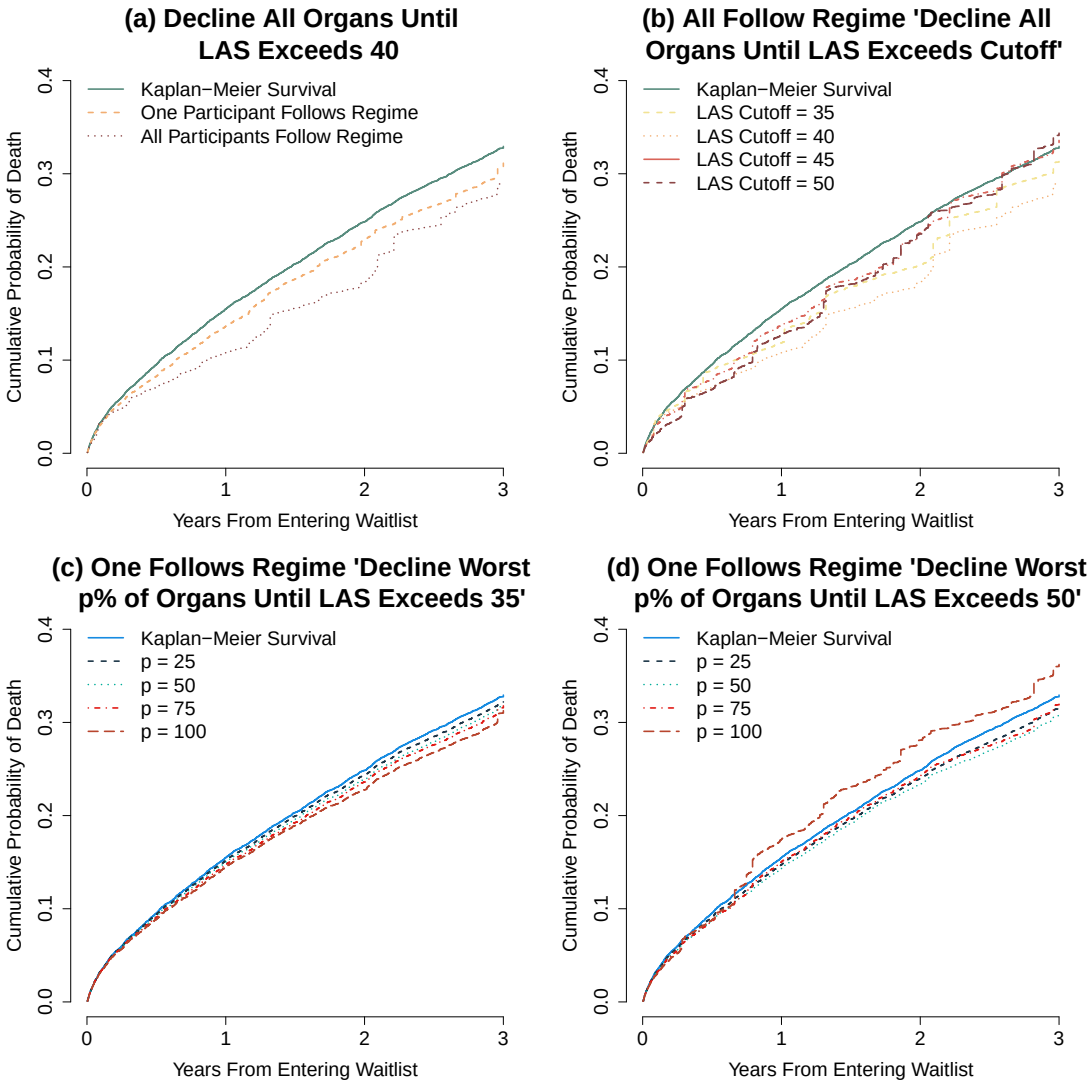

Figure 2.1: Chapter 2 Application Results

depends on whether other patients follow the proposed regime. Specifically, we introduced a novel IPCW-based estimator developed to test the efficacy of a treatment regime when either only a single individual uses a strategy versus the efficacy when the entire population uses a strategy. Although we restricted our attention to the extreme cases where either only one patient or all patients use a strategy, we could, in principle estimate the causal effect for intermediate cases (e.g., 50% of the population adopts the strategy) using simple modifications to the method.

The method relies heavily on correctly specifying the model for patients' probability of accepting organs. However, the method is attractive because many other processes need not be modeled at all to obtain reasonable estimates of the anticipated survival for following different regimes. In contrast to commonly used methods, we need not specify models for the stochastic organ arrival process, patient additions to the waiting list, the distribution of patient characteristics over time, survival on the waiting list in the absence of transplantation, or for post-transplant survival, as is the case for the thoracic simulated allocation model.

Although the method was developed in the context of treatment regimes for accepting organ transplants, an area in which data are publically available, the method is relevant for many other to other applications. We could, for example, use the proposed method to develop strategies on how to prioritize operating rooms in a hospital, provided that we have access to an observational data set and can devise a means to estimate the probability of observing treatment history in the observed data and in the counterfactual world.

The results of the simulation and the application demonstrate the care an analyst must use in specifying the target of estimation when attempting to estimate the efficacy of a treatment regime when individuals are competing for treatment. In particular, we demonstrated that substantively different conclusions on the effectiveness of a policy for declining cadaveric organs can be reached depending on whether or not others on the waiting list adopt the same policy. We did not make any attempt in this manuscript to identify an optimal treatment regime that would be of the greatest benefit to an individual, or a (possibly different) treatment regime that would be of the greatest benefit to the population. We plan to address this issue in future work.

Table 2.2: Chapter 2 Application Results

Plot	Which Organs to Decline	LAS Threshold	Who Follows	1 Year	2 Years	3 Years
(a)	All	40	One	-1.8%(0.43)	-2.0%(0.91)	-1.8%(1.31)
	All	40	All	-4.7%(1.63)	-6.4%(1.93)	-3.7%(2.11)
(b)	All	35	All	-3.6%(1.60)	-4.7%(1.85)	-1.4%(2.09)
	All	40	All	-4.7%(1.63)	-6.4%(1.93)	-3.7%(2.11)
	All	45	All	-1.7%(1.91)	-1.2%(2.24)	0.6%(2.27)
	All	50	All	-2.7%(1.92)	-1.3%(1.98)	1.4%(1.97)
(c)	Worst 25%	35	One	-0.3%(0.08)	-0.5%(0.15)	-0.7%(0.17)
	Worst 50%	35	One	-0.5%(0.09)	-1.0%(0.15)	-1.0%(0.27)
	Worst 75%	35	One	-0.8%(0.12)	-1.3%(0.31)	-1.2%(0.65)
	All	35	One	-1.0%(0.20)	-2.1%(0.37)	-1.7%(1.00)
(d)	Worst 25%	50	One	-0.8%(0.19)	-0.9%(0.35)	-1.3%(0.37)
	Worst 50%	50	One	-1.2%(0.44)	-1.5%(0.63)	-1.9%(0.64)
	Worst 75%	50	One	-0.5%(0.89)	-0.5%(1.11)	-0.7%(1.36)
	All	50	One	2.0%(1.10)	3.2%(1.45)	3.3%(1.70)

Difference from Un-weighted Kaplan-Meier Survival(S.E.) in probability of death for following the treatment regime. Negative numbers indicate a decreased cumulative probability of death. All regimes have the form "Decline organs while LAS $<$ LAS threshold." Estimates differ based on whether we assume one patient follows the regime or all patients follow the regime. The columns indicate which organs should be declined, the LAS threshold, and whether one or all patients are assumed to follow the regime.

Chapter 3

Estimating Causal Effects from a Randomized Controlled Trial when Noncompliance is Measured with Error

3.1 Chapter 3 Introduction

Twenty years ago, Benowitz and Henningfield (1994) argued the addictive properties of cigarettes could be eliminated if the nicotine content were reduced to 0.4-0.5 milligrams (mg) per gram of tobacco. In the United States, the Family Smoking Prevention and Tobacco Control Act provides the Food and Drug Administration (FDA) with the regulatory authority to limit the nicotine content of cigarettes to lower levels (but not zero) if such a regulation is likely to improve public health. As smoking remains the United States' leading cause of preventable death (U.S. Department of Health and Human Services, 2014), nicotine reduction could have a substantial public health impact. However, evidence for the effectiveness of such a policy is limited.

We recently reported the results of The Center for the Evaluation of Nicotine in Cigarettes, project 1 (CENIC-p1), a 6-week randomized trial evaluating the effect of nicotine reduction on tobacco use and dependence (Donny *and others*, 2015). Current

smokers ($n = 839$) were randomized equally to one of seven groups consisting of a usual brand control condition or experimental cigarettes with nicotine content ranging from 15.8 mg per gram of tobacco (normal nicotine controls) to 0.4 mg per gram of tobacco. In addition, the investigators included a group that received cigarettes with 0.4 mg of nicotine per gram of tobacco with high tar to understand the effect of tar yield on cigarette use and dependence when nicotine content is reduced. Participants were instructed to smoke only those cigarettes provided in the trial and were considered non-compliant if they smoked cigarettes not provided by the trial (i.e., non-study commercial cigarettes). Although they were not given incentives to avoid smoking non-study commercial cigarettes, they were encouraged to honestly report their smoking behavior and were allowed to complete the trial regardless of compliance. During week 6 of the study, smokers randomized to the lowest nicotine condition had significantly reduced tobacco use, dependence, and nicotine exposure compared to the usual brand and normal nicotine control conditions.

The results of CENIC-p1 provide empirical support for nicotine reduction as a regulatory strategy, but they must be interpreted cautiously due to substantial noncompliance to randomized treatment assignment. For example, among participants randomized to smoke very low nicotine content (VLNC) cigarettes (cigarettes with 0.4 mg of nicotine per gram of tobacco), 39% reported smoking at least 1 non-study cigarette during week 6, and 80% reported smoking at least 1 non-study cigarette at some point during the trial. A per protocol analysis, i.e., analyzing only compliant participants, is problematic because compliance status is confounded, and compliers may differ systematically from non-compliers. The primary analysis of CENIC-p1 followed the intention-to-treat (ITT) principle and analyzed the data from all participants according to their randomized treatment assignment regardless of their compliance. An ITT analysis provides an unbiased estimator of the effect of a treatment or intervention when it is used in an environment (e.g., target population, level of non-compliance, etc.) similar to the clinical trial environment (Hernán and Hernández-Díaz, 2012). However, if the nicotine content of cigarettes were limited by regulation, and smokers no longer had legal access to standard commercial cigarettes, the effect of nicotine reduction on smoking behavior may be different than in the trial.

Our goal is to estimate the effect of smoking VLNC cigarettes on cigarette consumption and other measures of smoking behavior (dependence, withdrawal, etc.) in the hypothetical world where a regulatory body has reduced the nicotine content of cigarettes, and normal nicotine content commercial cigarettes are no longer available. In the language of clinical trials, we wish to estimate the effect of smoking VLNC cigarettes in the presence of complete compliance, i.e., the causal effect (Bellamy *and others*, 2007). Methods for estimating the causal effect of an intervention in the presence of noncompliance are well-established and include inverse probability of compliance weighted (IPCW) estimators (Cain and Cole, 2009; Hernán and Robins, 2006), principal stratification (Frangakis and Rubin, 2002), structural nested models estimated by G-estimation (Robins, 1994), and instrumental variable approaches (Angrist *and others*, 1996).

Existing methods for estimating causal effects in the presence of noncompliance assume that investigators know, without error, whether or not a participant was compliant. In the context of randomized tobacco trials, like CENIC-p1, self-reported compliance is subject to error and recall bias, and analyzing biomarkers of nicotine exposure has been suggested as an alternate approach to identify non-compliant participants (Benowitz *and others*, 2015). One recent study (Denlinger *and others*, 2016) evaluating biomarkers of nicotine exposure in participants exclusively smoking cigarettes with 0.4 mg per gram of tobacco found that the 95th percentile for total nicotine equivalents (TNEs, a biomarker of short-term nicotine exposure that measures most nicotine metabolites) was 6.41 nmol/ml. Yet among the CENIC-p1 participants randomized to the 0.4 mg per gram of tobacco arm, 63% of participants who self-reported full compliance during week 6 had TNE greater than 6.41 nmol/ml (Nardone *and others*, 2016). This demonstrates that self-reported compliance can substantially misclassify whether or not participants were compliant to their randomized treatment assignment. Although certain biomarkers (e.g., TNE) may suggest that a participant's self-reported compliance status is incorrect, no biomarker of nicotine exposure perfectly discriminates between compliers and non-compliers.

We propose a novel estimator of the causal effect from a randomized clinical trial when compliance status is measured with error. In contrast to existing methods, our estimator explicitly accounts for the potential for misclassification of compliers and

non-compliers. Although we treat compliance status as an unobserved variable, we show how to weight participants by the product of their probability of compliance given the observed data and the inverse probability of compliance given confounders, resulting in a consistent and asymptotically normal estimator of the causal effect. Our simulation results illustrate that in finite samples our estimator outperforms *ad hoc* causal methods which ignore the error in compliance status by using either self-reported data or by using an estimated indicator of compliance. When there is a perfect discriminator of compliers and non-compliers, our estimator reduces to the standard IPCW estimator.

3.2 Causal Effect Estimators

3.2.1 Potential Outcomes and Target of Inference

We consider a hypothetical randomized clinical trial, where $A = 1, 2, \ldots, r$ denotes the treatment group, which we assume is randomized. Let Z be a measure (without error) of noncompliance with $Z = 0$ indicating full compliance and increasing Z indicating greater noncompliance. For example, Z may be the number of non-study commercial cigarettes smoked in week 6 of CENIC-p1 or the number of pills not taken in a therapeutic clinical trial. Define the compliance indicator $C = I(Z = 0)$, and note that Z and C are not directly observed if noncompliance is measured with error. Define $Y^*(a, z)$ to be the outcome of a randomly-selected participant if, possibly contrary to fact, we set $A = a$ and $Z = z$. Because for each participant we do not observe $Y^*(a, z)$ for all a and z, $Y^*(a, z)$ is a potential outcome. For CENIC-p1, $Y^*(a, z)$ is the number of study cigarettes with nicotine content a smoked per day in week 6 of the study if the participant were to smoke z non-study cigarettes per day. The target of inference is $\mu(a, 0) - \mu(a', 0) = E\{Y^*(a, 0) - Y^*(a', 0)\}$, the expected difference of the outcome among randomized treatment groups a and a' if all participants were to be compliant. In the context of mediation literature, $\mu(a, 0) - \mu(a', 0)$ is known as the controlled direct effect (Pearl, 2001), that is, the treatment effect when the mediator, number of non-study cigarettes, is set at the fixed value of 0.

3.2.2 Observed Data

Let Y be the observed outcome for a randomly-selected participant. Define the self-reported compliance indicator variable D, with $D = 1$ indicating the participant reports full compliance and $D = 0$ indicating that the participant reports any noncompliance. Let X be a vector of patient variables, and let B be a biomarker indicating exposure to the treatment A. In the context of CENIC-p1, Y is the number of study cigarettes smoked per day during week 6 of the trial, B is a biomarker of nicotine exposure (e.g., TNE or cotinine) measured during week 6, $D = 1$ if the participant reports smoking 0 non-study cigarettes during week 6, and $D = 0$ if the participant reports smoking any non-study cigarettes during week 6. Note that participants self-report D, and this may be subject to error and recall biases.

3.2.3 Identifying Assumptions

To relate the distribution of the observed data to the distribution of the potential outcome $Y^*(a, 0)$ in the case where C is observed, we make the following identifying assumptions (Robins and Hernán, 2008). First, we assume that we have measured enough covariates such that the compliance status is conditionally ignorable. That is, we assume the probability that a participant is compliant depends only on the observed covariates X and A and not additionally on any potential outcomes; this implies that $E\{C|A, X, Y^*(a, 0)\} = E(C|A, X)$ (no unmeasured confounders assumption). Although there may be additional variables associated with C, e.g. the biomarker B, we assume that there are no additional confounders aside from X. Second, we assume that $E(C|A, X) > 0$ for all X and A, that is, there is positive probability of complying with the randomized treatment assignment within all levels of the confounders (positivity assumption). Finally, we assume that if $Z = 0$ and $A = a$, then $Y = Y^*(a, 0)$, that is, if a participant is compliant with the trial protocol, then her observed outcome is the same as it would be if the participant were forced to be compliant with the trial protocol (consistency assumption). When C is unobserved, additional assumptions will be necessary and will be stated where required.

3.2.4 Proposed Estimators

We have stressed that C may not be directly observed due to measurement error or misclassification, but assume for now that $E(C|A, B, X, Y, D)$ and $E(C|A, X)$ are known. We discuss in Section 3.3 how these expectations can be estimated even though C is unobserved. We can estimate $\mu(a, 0)$ by solving the following estimating equation:

$$\sum_{i=1}^{n} \frac{E\left(C_i|A_i, B_i, X_i, Y_i, D_i\right)}{E\left(C_i|A_i, X_i\right)} \left\{Y_i - \mu(a, 0)\right\} I(A_i = a) = 0. \tag{3.1}$$

A similar estimator could be constructed for $\mu(a', 0)$, and the difference in those estimators could be used to estimate the treatment effect.

The estimating function with weights $\frac{E(C|A,B,X,Y,D)}{E(C|A,X)}$ is similar to a standard IPCW estimator with weights $\frac{C}{E(C|A,X)}$, but we have replaced the numerator with the conditional expected value of compliance instead of an indicator variable for compliance status. Note that if all participants self-reported compliance without error, or if there exists a biomarker that can perfectly discriminate compliers from non-compliers, then $E\left(C|A, B, X, Y, D\right)$ equals 0 or 1, and the estimating function in Equation (3.1) simplifies to the standard IPCW estimating function. Although it is not obvious that we can obtain valid inference without observing C, we show in Section 3.4 that, under suitable regularity conditions, $\hat{\mu}(a, 0)$, the solution to the estimating equation, is a consistent and asymptotically normal estimator of $\mu(a, 0)$. Because our estimator has an expectation, rather than an indicator variable, in the numerator to account for potential misclassification, we refer to the estimator as the Compliance Unsure RE-weighted estimator, or CURE estimator.

3.3 Estimating the Weights

In practice, $E(C|A, B, X, Y, D)$ and $E(C|A, X)$ are usually unknown and must be estimated. To estimate these, we begin by re-writing $E(C|A, B, X, Y, D)$ as a function of components that can be estimated directly from the observed data. We then show how auxiliary data, if available, can be used to obtain a more precise estimate of $E(C|A, B, X, Y, D)$. Finally, we discuss how $\hat{E}(C|A, B, X, Y, D)$, the estimate of $E(C|A, B, X, Y, D)$, can be used to estimate $E(C|A, X)$.

3.3.1 Estimating the Numerator of the Weights

First, using Bayes' Theorem, we can write $E(C|A=a,B=b,X=x,Y=y,D=d)$ as:

$$\frac{f(b|a,x,y,d,c=1;\xi)\cdot\rho(a,x,y,d;\alpha)}{f(b|a,x,y,d,c=1;\xi)\cdot\rho(a,x,y,d;\alpha)+f(b|a,x,y,d,c=0;\xi)\cdot\{1-\rho(a,x,y,d;\alpha)\}}, \tag{3.2}$$

where f is the conditional density of B given A, X, Y, D, and C indexed by parameter vector ξ, and $\rho(a,x,y,d;\alpha) = \Pr(C=1|A=a,X=x,Y=y,D=d;\alpha)$ indexed by parameter vector α. Rewriting the expectation shifts the goal from estimating the conditional expectation of C to estimating the conditional distribution of $B|A,X,Y,D,C$. Note that B, A, X, Y and D are all observed random variables, which allows us to directly estimate the density of $B|A,X,Y,D$ as the mixture density

$$\begin{aligned} g(b|a,x,y,d;\xi,\alpha) =& \rho(a,x,y,d;\alpha)\cdot f(b|a,x,y,d,c=1;\xi)+ \\ & \{1-\rho(a,x,y,d;\alpha)\}\cdot f(b|a,x,y,d,c=0;\xi). \end{aligned} \tag{3.3}$$

Thus, although we do not observe C, we can estimate $E(C|A,B,X,Y,D)$ by estimating the conditional density of $B|A,X,Y,D$. The maximum likelihood estimators of ξ and α solve the score equations

$$\sum_{i=1}^{n}\frac{\partial}{\partial(\xi^T,\alpha^T)^T}\log g(B_i|A_i,X_i,Y_i,D_i;\xi,\alpha)=0. \tag{3.4}$$

As is frequently the case with mixture distributions, Equation (3.4) may be difficult to solve directly. In that case we can find the maximum likelihood estimates using the EM algorithm (Dempster *and others*, 1977). In Appendix B, we give details of the EM algorithm updates for ξ and α.

Equations (3.2) - (3.4) can sometimes be simplified based on the scientific problem. For example, in some applications it may be reasonable to simplify the modeling assumptions of the conditional density of B. In particular, according the directed acyclic graph (DAG) in Appendix B, which is one plausible DAG for the CENIC-p1 data, B may be conditionally independent of X given A, Y and C. We note that this assumption is testable using observed data so the data analyst does not need to a priori assume the correct causal structure. Additionally, it may be reasonable to assume that if $D=0$,

i.e., the participant reports noncompliance with the study protocol, then $C = 0$ without error. That is, participants may not erroneously report noncompliance because in most trials there is usually no incentive to be non-compliant. This would imply that $E(C|A, B, X, Y, D = 0) = 0$.

3.3.2 Incorporating Compliance Information from an Auxiliary Study

Estimating mixture distributions is challenging in practice due to difficulties in identifying the underlying component densities. An advantage to estimating the mixture distribution of $B|A, X, Y, D$ for CENIC-p1 is the presence of an auxiliary study to evaluate biomarkers of nicotine exposure in fully compliant participants. Denlinger *and others* (2016) present data on biomarkers of nicotine exposure for 23 smokers who volunteered to be sequestered in a hotel for 4 nights with access to only cigarettes with 0.4 mg nicotine per gram of tobacco. These participants are known to be compliant, and their data can be used in conjunction with the data from CENIC-p1 to estimate the density of the biomarker in compliers. This will enhance our ability to identify the underlying components of the mixture distribution for $B|A, X, Y, D$. While these auxiliary data may seem unique to CENIC-p1, similar data arise in other settings. For example, pharmacokinetic/pharmacodynamic data from early-phase clinical trials could be used to help identify compliers in a phase III therapeutic clinical trial. In our application we do not want to include these individuals' outcomes, Y, in estimation of the causal effect due to differences in smoking behavior between participants in the auxiliary and primary studies, but we do expect the distribution of $B|A, X, Y, D = 1, C = 1$ to be consistent across studies. This is known as the *transportability* assumption in the measurement error literature (Carroll *and others*, 2006).

Let n_k denote the number of participants in the auxiliary study, let $m = n + n_k$, and define the indicator variable K that equals 1 if the participant is included in the auxiliary data or 0 if the participant is included in the main trial. We can incorporate the auxiliary data when estimating ξ and α by solving the score equations

$$\sum_{i=1}^{m} \frac{\partial}{\partial(\xi^T, \alpha^T)^T} \{(1 - K_i) \cdot \log g(B_i|A_i, X_i, Y_i, D_i; \xi, \alpha) + K_i \cdot \log f(B_i|A_i, X_i, Y_i, d = 1, c = 1; \xi)\} = 0. \quad (3.5)$$

3.3.3 Estimating the Denominator of the Weights

In most applications, the denominator of the weights will be unknown and must be estimated. Because the denominator must be between 0 and 1, we specify a regression model $E(C_i|A_i, X_i) = \pi_i(\beta) = g^{-1}\left\{\beta_0 + X_i^T\beta_1 + I(A_i = 2)\beta_2 + \cdots + I(A_i = r)\beta_r\right\}$, where g is a link function that maps from (0, 1) to $\mathbb{R}$, such as the logit or probit link, and $\beta = (\beta_0, \beta_1^T, \beta_2, \ldots, \beta_r)^T$ is a vector of unknown regression coefficients. If $E(C|A, B, X, Y, D)$ were known, we could estimate β by solving the estimating equation

$$\sum_{i=1}^{m}(1 - K_i)\frac{\{E(C_i|A_i, B_i, X_i, Y_i, D_i; \xi, \alpha) - \pi_i(\beta)\}}{\pi_i(\beta)\{1 - \pi_i(\beta)\}}\frac{\partial\pi_i(\beta)}{\partial\beta^T} = 0. \tag{3.6}$$

That is, $E(C|A, B, X, Y, D; \xi, \alpha)$ is the "response" of the regression model. Note that β can be estimated using standard software, for example, using the `glm` function in `R`. Because $E(C|A, B, X, Y, D; \xi, \alpha)$ is between 0 and 1, this is analogous to modeling proportions in a logistic or probit model. In the case that ξ and α are unknown, we can stack Equations (3.5) and (3.6) and solve jointly, which is equivalent to replacing $E(C|A, B, X, Y, D; \xi, \alpha)$ in Equation (3.6) with the estimated expectation $E(C|A, B, X, D, Y, D; \hat{\xi}, \hat{\alpha})$.

3.4 Asymptotic Properties of the CURE Estimator

In discussing the asymptotic properties of the proposed estimator, for simplicity we assume there are no auxiliary data of the type described in Section 3.3.2 and consider only a single-arm trial with $a = 1$ for all participants, but the results easily generalize to multi-arm trials. Under the assumptions in Section 3.2.3, the estimating function has expectation equal to 0. The key to demonstrating this is to note that in expectation, our proposed estimator is equivalent to an IPCW estimator in which the compliance

status is known without error:

$$
\begin{aligned}
& E\left[\frac{E\left(C_i|B_i,X_i,Y_i,D_i\right)}{E\left(C_i|X_i\right)}\left\{Y_i-\mu(1,0)\right\}\right] \\
&= E\left[\frac{C_i}{E\left(C_i|X_i\right)}\left\{Y_i-\mu(1,0)\right\}\right] \\
&= E\left[\frac{E\left\{C_i|X_i,Y_i^*(1,0)\right\}}{E\left(C_i|X_i\right)}\left\{Y_i^*(1,0)-\mu(1,0)\right\}\right] \\
&= E\left[\frac{E(C_i|X_i)}{E\left(C_i|X_i\right)}\left\{Y_i^*(1,0)-\mu(1,0)\right\}\right]=0. \qquad (3.7)
\end{aligned}
$$

The 1st equality follows from iterated expectation. At this step, the argument of the expectation is now equivalent to the case when C is known without error, and the remaining equalities follow from assumptions stated in Section 3.2.3: the 2nd follows from the consistency assumption and iterated expectation, and the 3rd follows from the no unmeasured confounders assumption. Note that the result in Equation (3.7) hold even if B is null. That is, we do not need to measure a biomarker of exposure and could replace $E(C_i|B_i,X_i,Y_i,D_i)$ with $E(C_i|X_i,Y_i,D_i)$ and the estimating function would still have expectation equal to zero. Nevertheless, conditioning on B allows us to incorporate auxiliary compliance data as described in Section 3.3.2. Furthermore, including a biomarker of compliance improves the discrimination between the compliers and non-compliers which will improve the computational stability of the estimates in the mixture distribution in Equation (3.3).

We can simultaneously estimate $\mu(1,0),\xi,\alpha$, and β by stacking the estimating equations given in Equations (3.1), (3.5), and (3.6). Let $\mathbf{Z}_i=(A_i,B_i,X_i,Y_i,D_i)$ be the observed data on participant i and $\sum_{i=1}^n\psi_i\left\{\mathbf{Z}_i;\mu(1,0),\xi,\alpha,\beta\right\}$ denote the stacked estimating function. We showed above that the first component of $\psi_i\left\{\mathbf{Z}_i;\mu(1,0),\xi,\alpha,\beta\right\}$ has expectation 0; the components corresponding to $(\xi^T,\alpha^T)^T$ and β have expectation 0 due to being score functions of a log likelihood and of a generalized linear model, respectively. The fact that the stacked estimating function has expectation 0 implies that, under suitable regularity conditions,

$$
\sqrt{n}\left[\left\{\hat{\mu}(1,0),\hat{\xi}^T,\hat{\alpha}^T,\hat{\beta}^T\right\}^T-\left\{\mu(1,0),\xi^T,\alpha^T,\beta^T\right\}^T\right]\xrightarrow{D}N\left(0,U^{-1}V(U^{-1})^T\right),
$$

where $V=E(\left[\psi_i\left\{\mathbf{Z}_i;\mu(1,0),\xi,\alpha,\beta\right\}\right]\left[\psi_i\left\{\mathbf{Z_i};\mu(1,0),\xi,\alpha,\beta\right\}\right]^T)$ and
$U=-E\left[\frac{\partial\psi_i\{\mathbf{Z}_i;\mu(1,0),\xi,\alpha,\beta\}}{\partial\{\mu(1,0),\xi^T,\alpha^T,\beta^T\}^T}\right]$. The sandwich covariance matrix $U^{-1}V(U^{-1})^T$ can be

estimated using the empirical averages for U and V (see, for example, Stefanski and Boos (2002)) or with the bootstrap (Efron, 1979).

Note that unlike IPW estimators when C is known where only the model for $E(C_i|X_i)$ must be correctly specified, the CURE estimator also relies on correctly specifying the distribution of the mixture components in Equation (3.3) to obtain consistent and asymptotically normal estimators.

We compare the relative efficiency of the CURE estimator to the standard IPCW estimator when compliance is observed in order to understand the consequences of measuring compliance with error. If $E(C|X)$ and $E(C|B, X, Y, D)$ are known and do not need to be estimated, then the CURE estimator is more efficient than the standard IPCW estimator with weights $\frac{C}{E(C|X)}$. To see this, first note that

$$\begin{aligned} &E\left(\frac{\partial}{\partial\{\mu(1,0)\}}\left[\frac{C_i}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right]\right) \\ &= E\left(\frac{\partial}{\partial\{\mu(1,0)\}}\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right]\right), \end{aligned}$$

so the difference in the limiting variance of the estimators is due to differences in the variances of the estimating function. Next, we can write

$$\begin{aligned} &\text{var}\left[\frac{C_i}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right] \\ &= \text{var}\left[\frac{C_i-E(C_i|B_i,X_i,Y_i,D_i)+E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right]. \end{aligned}$$

Then, because

$$\text{cov}\left[\frac{C_i-E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}, \frac{E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right]$$

$$\begin{aligned} &= E\left(\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)-E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right]\times\right. \\ &\quad \left.\frac{E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\{Y_i-\mu(1,0)\}\right) = 0 \end{aligned}$$

by iterated expectation, the variance of the estimating function with weights $\frac{C}{E(C|X)}$ is

$$\begin{aligned}
&\text{var}\left[\frac{C_i}{E(C_i|X_i)}\left\{Y_i-\mu(1,0)\right\}\right] \\
=&\text{var}\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\left\{Y_i-\mu(1,0)\right\}\right]+ \\
&\text{var}\left[\frac{C_i-E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\left\{Y_i-\mu(1,0)\right\}\right] \\
\geq&\text{var}\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)}{E(C_i|X_i)}\left\{Y_i-\mu(1,0)\right\}\right].
\end{aligned}$$

Thus, if all expectations are known and do not need to be estimated, the CURE estimator is more efficient asymptotically than the standard IPCW estimator. To gain some intuition for why this occurs, consider the case where compliance has no effect on the outcome: the CURE estimator gains efficiency by simply taking a sample average of the outcome among participants randomized to group a to estimate $\mu(a,0)$, whereas the IPCW estimator excludes participants who are non-compliant even though compliance has no effect on the outcome. As the effect of compliance on the outcome strengthens, $E(C|B,X,Y,D)$ approaches an indicator function and the CURE estimator approaches the standard IPCW estimator. In general, the CURE estimator borrows more data from the non-compliers as the effect of compliance decreases, which increases efficiency over the IPCW estimator.

A natural question is how estimating the weights impacts the variances of the estimators. Here we use notation consistent with the generalized linear model notation introduced previously, and we remind the reader that $E(C|X)$ can be written as $\pi(\beta)$. When the weights are $\frac{C}{\pi(\beta)}$, and β must be estimated jointly with $\mu(1,0)$, the asymptotic variance of $\hat{\mu}(1,0)$ is

$$E\left[\frac{\left\{Y_i^*(1,0)-\mu(1,0)\right\}^2}{\pi_i(\beta)}\right]-H_1H_2^{-1}H_1^T,$$

where $H_1=E\left[\frac{Y_i^*(1,0)-\mu(1,0)}{\pi_i(\beta)}\frac{\partial\pi_i(\beta)}{\partial\beta}\right]$ and $H_2=E\left[\frac{1}{\pi_i(\beta)\{1-\pi_i(\beta)\}}\frac{\partial\pi_i(\beta)}{\partial\beta^T}\frac{\partial\pi_i(\beta)}{\partial\beta}\right]$. This interesting result shows that the variance of $\hat{\mu}(1,0)$ with weights $\frac{C}{\pi(\beta)}$ is reduced when β is estimated compared to when β is known (Lunceford and Davidian, 2004). When the weights are $\frac{E(C|B,X,Y,D;\xi,\alpha)}{\pi(\beta)}$, when ξ,α, and β must be estimated jointly with $\mu(1,0)$, and when their are no auxiliary data to use in estimating the parameters of the mixture

density (3.3), then the large sample variance of $\hat{\mu}(1,0)$ is

$$E\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)^2}{\pi_i(\beta)^2}\left\{Y_i-\mu(1,0)\right\}^2\right]+$$
$$2\left[\left(-H_3H_4^{-1}+H_1H_2^{-1}H_5H_4^{-1}\right)\quad\left(-H_1H_2^{-1}\right)\right]\begin{bmatrix}H_6^T\\H_7^T\end{bmatrix}+$$
$$\begin{bmatrix}\left(-H_3H_4^{-1}+H_1H_2^{-1}H_5H_4^{-1}\right)^T\\\left(-H_1H_2^{-1}\right)^T\end{bmatrix}^T\begin{bmatrix}H_4&H_8\\H_8^T&H_9\end{bmatrix}\begin{bmatrix}\left(-H_3H_4^{-1}+H_1H_2^{-1}H_5H_4^{-1}\right)^T\\\left(-H_1H_2^{-1}\right)^T\end{bmatrix} \tag{3.8}$$

where

$$H_3=-E\left[\frac{Y_i-\mu(1,0)}{\pi_i(\beta)}\frac{\partial E(C_i|B_i,X_i,Y_i,D_i)}{\partial(\xi^T,\alpha^T)}\right]$$
$$H_4=E\left[\frac{\partial\log g(B_i|X_i,Y_i,D_i;\xi,\alpha)}{\partial(\xi^T,\alpha^T)^T}\frac{\partial\cdot\log g(B_i|X_i,Y_i,D_i;\xi,\alpha)}{\partial(\xi^T,\alpha^T)}\right]$$
$$H_5=-E\left[\pi_i(\beta)\left\{1-\pi_i(\beta)\right\}\frac{\partial\pi_i(\beta)}{\partial\beta^T}\frac{\partial E(C_i|B_i,X_i,Y_i,D_i)}{\partial(\xi^T,\alpha^T)}\right]$$
$$H_6=E\left[\frac{C_i\left\{Y_i^*(1,0)-\mu(1,0)\right\}}{\pi_i(\beta)}\frac{\partial\cdot\log g(B_i|X_i,Y_i,D_i;\xi,\alpha)}{\partial(\xi^T,\alpha^T)}\right]$$
$$H_7=E\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)\left\{Y_i-\mu(1,0)\right\}\left\{E(C_i|B_i,X_i,Y_i,D_i)-\pi_i(\beta)\right\}}{\pi_i(\beta)^2\left\{1-\pi_i(\beta)\right\}}\frac{\partial\pi_i(\beta)}{\partial\beta}\right]$$
$$H_8=E\left[\frac{E(C_i|B_i,X_i,Y_i,D_i)-\pi_i(\beta)}{\pi_i(\beta)\left\{1-\pi_i(\beta)\right\}}\frac{\partial\log g(B_i|X_i,Y_i,D_i;\xi,\alpha)}{\partial(\xi^T,\alpha^T)^T}\frac{\partial\pi_i(\beta)}{\beta}\right]$$
$$H_9=E\left[\frac{\left\{E(C_i|B_i,X_i,D_i,Y_i)-\pi_i(\beta)\right\}^2}{\left[\pi_i(\beta)\left\{1-\pi_i(\beta)\right\}\right]^2}\frac{\partial\pi_i(\beta)}{\partial\beta^T}\frac{\partial\pi_i(\beta)}{\partial\beta}\right]$$

and H_1 and H_2 were defined previously. The last term in (3.8) is positive because it is a quadratic form of a positive semi-definite matrix, but the middle term does not have this property and is neither clearly positive nor clearly negative under all conditions. Thus, although estimating the weights for the IPCW estimator is guaranteed to increase the asymptotic efficiency of $\hat{\mu}(1,0)$, there is no such guarantee for the CURE estimator. If C were observed and $E(C|B,X,Y,D)$ were estimated using a regression model in the CURE estimator, then we could make a definitive statement about the impact of estimating $(\xi^T,\alpha^T)^T$ on the limiting variance of $\mu(1,0)$, but this is not possible when C is not observed and we used the approach described in Section 3.3. Also note that the information matrix H_4 will contain more information when auxiliary data are

incorporated as described in Section 3.3.2, but this may be beneficial only for estimation of the mixture density (3.3) in small samples, not for asymptotic efficiency of $\hat{\mu}(1,0)$.

3.5 Simulation Study

We designed a simulation study to test the finite-sample properties of the proposed estimator. The `R` code for the simulation is available at `https://github.com/jeffrey-boatman/cure-estimator`. For simplicity, we consider a scenario in which all participants are assigned a single treatment, $A = 1$, and only estimate $\mu(1,0)$, rather than a difference in means between two treatment groups. To facilitate data generation, define C' as a latent continuous measure of compliance. We generated (C', X, Y) from a multivariate normal distribution with mean vector $(0, 10, 16)^T$ and covariance matrix $\Sigma = \begin{pmatrix} 1.000 & -0.573 & -0.139 \\ -0.573 & 2.000 & 1.715 \\ -0.139 & 1.715 & 3.000 \end{pmatrix}$. We define the compliance indicator $C = I\left\{C' > \Phi^{-1}(0.80)\right\}$, where Φ is the standard normal cumulative distribution function. This gives $Pr(C = 1) = 0.20$, consistent with the preliminary estimates of the compliance rate from CENIC-p1 (Nardone *and others*, 2016). We simulated $B \sim N(-9.3 - 0.8 \cdot C + 0.7 \cdot Y, \sigma^2)$ with 2 values of σ^2, 0.818 and 0.663, to give an area under the ROC curve of 0.8 or 0.9, respectively, for discriminating between compliers and non-compliers. We let $D = H^{1-C}$, where H is a Bernoulli random variable with success probability 0.3 independent of other data, so that those truly compliant ($C = 1$) always self-report compliance and for non-compliant participants ($C = 0$) H is an indicator of whether or not non-compliance was reported with error. The data generated are consistent with the DAG shown in the Appendix B, which is one possible DAG for the CENIC-p1 data. Note that the DAG implies that B and X are conditionally independent given C and Y (and A, which here has only one level).

We considered sample sizes of 225 (roughly the number of participants randomized to the VLNC cigarettes in CENIC-p1), 500, and 1,000 and also included data from an auxiliary study in which participants are known to be compliant as described in Section 3.3.2 equal to 10% of the size of the main clinical trial.

We compared 5 estimators of $\mu(1,0)$: (1) a per protocol estimator based on self-reported compliance; (2) a self-reported inverse probability weighted (IPW) estimator with weights equal to $\frac{D}{\hat{E}(D|X)}$; (3) an IPW estimator with weights equal to $\frac{C}{\hat{E}(C|X)}$; (4) a "cutoff" IPW estimator that first estimates $E(C|B,X,Y,D)$ using the methods described in Section 3.3.1, defines $\hat{C} = \hat{E}(C|B,X,Y,D) > 0.5$, and then uses the weights $\frac{\hat{C}}{\hat{E}(\hat{C}|X)}$; and (5) the CURE estimator with weights $\frac{\hat{E}(C|B,X,Y,D)}{\hat{E}(C|X)}$. Although we have argued the IPW estimator cannot be used in CENIC-p1, we include it for comparison to illustrate the cost of relying on imperfect measures of compliance. We assumed that $E(C|X,Y,D=0) = 0$, and observations with $D = 0$ did not contribute to estimation of the mixture distribution. To estimate $E(C|B,X,Y,D=1)$ in the cutoff IPW and CURE estimators, we assumed simple linear regression models with normal residuals for $B|Y,D=1,C=1$ and $B|Y,D=1,C=0$; to estimate $E(C|X,Y,D=1)$ we assumed a generalized linear model with probit link. To improve computation time, we used a single set of starting values for the EM algorithm which were estimated parameters from models fit using the actual compliance C. In applications when C is unknown to the analyst and cannot be used to generate starting values, the EM algorithm may require multiple iterations with different starting values to find the global MLE, but the simulation nevertheless gave good results using only this one set of starting values for each iteration. For the self-reported IPW, cutoff IPW, and CURE estimators, the denominator of the weights was estimated using a generalized linear model with probit link where the outcome is the numerator of the weights. We used the bootstrap percentile method with 1,000 bootstrap re-sampled data sets to compute 95% confidence intervals.

Table 3.1 shows the simulation results. Overall, the CURE estimator has very small bias for both AUC of 0.8 and 0.9. With AUC of 0.8, the CURE estimator has higher mean squared error than per protocol or IPW based on self-report, but with sample size 1,000 the mean squared error is smaller; with AUC of 0.9, the CURE estimator has lower mean squared error for sample sizes 500 and 1,000. The per protocol and self-report IPW estimators show bias that is not attenuated with increasing sample size and coverage probabilities which are not close to the nominal level. The cutoff IPW estimator has low bias, but, surprisingly, for each sample size and AUC level, the CURE estimator has much smaller mean squared error and coverage probability closer to the

nominal 0.95 level. Unsurprisingly, the CURE estimator has higher mean squared error than the IPW estimator, but the mean squared error of the CURE estimator approaches that of the IPW estimator as the AUC increases. The simulation results demonstrate that the CURE estimator has better small sample performance than per protocol and self-report IPW when there is potential for misclassification. Furthermore, the CURE estimator performs better than an *ad hoc* estimator that uses IPW with an estimated indicator variable of compliance.

3.6 Application to the CENIC Data

We applied the CURE estimator to estimate the causal effect of VLNC cigarettes on the number of cigarettes smoked per day using data from CENIC-p1. Although CENIC-p1 was a 6-week trial, for simplicity we are only concerned with compliance and outcomes collected in the last week. In this analysis, we let $A = 1$ if the participant was randomized to smoke VLNC cigarettes (0.4 mg nicotine per gram of tobacco, high and low tar groups combined) and let $A = 2$ if randomized to smoke usual brand cigarettes. All other notation in this application is defined in Section 3.2.

The goal of this analysis is to estimate the causal contrast $\mu(2,0) - \mu(1,0)$, the expected reduction in cigarettes smoked per day during week 6 if smoking only VLNC cigarettes versus smoking usual brand cigarettes. We estimate the causal effect by estimating $\mu(2,0)$ and $\mu(1,0)$ separately and taking their difference. The usual brand group is meant to represent smoking behavior with commercially available cigarettes and, in that sense, participants in this group were never treated as non-compliant, and $\mu(2,0)$ was estimated using the sample average of the total number of cigarettes smoked per day during week 6 (i..e. study plus non-study cigarettes). We consider the 4 estimators for $\mu(1,0)$ discussed in the simulation study (excluding IPW because C is unobserved) and include the ITT estimator for comparison.

As in the simulation, we assumed that $E(C|A,X,Y,D=0) = 0$, and participants with $D = 0$ did not contribute to estimation of the mixture distribution. Using the biomarker log(TNE) measured at week 6 as the (only) biomarker B of exposure, we estimated the probability of compliance for participants self-reporting compliance (i.e.,

$D = 1$) following the approach in Section 3.3.1. Specifically, in fitting the mixture distribution in Equation (3.3), we assume a simple linear regression model with normally distributed errors for $B|A = 1, Y, D = 1, C$ with no shared parameters between the different levels of C. As in the simulation, we assume that B and X are conditionally independent given A, Y and C, consistent with the DAG in Appendix B. We assumed a logistic regression model for $\Pr(C = 1|A = 1, X, Y, D = 1)$, where the confounders X included age, level of addiction (baseline cigarettes per day and log of TNE), measures of withdrawal (Minnesota Nicotine Withdrawal Scale at week 5 and maximum acute withdrawal), and satisfaction with and craving for VLNC (Cigarette Evaluation Scale and Questionnaire of Smoking Urges at week 5) and normal nicotine cigarettes (Questionnaire of Smoking Urges at Week 5). We incorporated the data for the 23 participants from Denlinger *and others* (2016) who were known to be compliant to aid in estimating the parameters of the mixture distribution as described in Section 3.3.2. Multiple sets of starting values were tried for the EM algorithm, and we used those values which gave the lowest negative log likelihood. We estimated the denominator $\Pr(C = 1|A = 1, X)$ following the approach of Section 3.3.3 using a logit link with the same predictors X described above. All confidence intervals were estimated using the non-parametric bootstrap percentile method with 1,000 bootstrap resamples.

For the VLNC group, 137 of 222 (61.7%) participants self-reported compliance during week 6. The left panel of Figure 3.1 shows a histogram of $B = \log(\text{TNE})$ for the self-reported compliers in the treatment group, the estimated mixture distribution, and the complier and non-complier component distributions, which supports our parametric assumptions for the components of the mixture distribution. The right panel shows the probability of compliance as a function of TNE and Y, the self-reported number of cigarettes per day. We estimated $\Pr(C = 1|A = 1, D = 1) = 0.376$, and $\Pr(C = 1|A = 1) = 0.224$, indicating a substantial proportion of self-reported compliers were non-compliant. Estimated coefficients and parameters for the numerator and denominator of the weights and 95% bootstrap confidence intervals can be found in Appendix B. We also include a table giving some summary statistics of baseline characteristics, confounders, and the biomarker week 6 log(TNE).

Table 3.2 shows the estimated causal effect of VLNC cigarettes on number of cigarettes smoked per day. The Cutoff IPW gives the most optimistic estimate of the causal effect

of the treatment, while the CURE estimate is more conservative. In contrast, the per protocol and self-report IPW estimators give similar and more modest estimates of the treatment effect. Although the CURE and Cutoff IPW estimates are similar, note that the length of the 95% confidence interval is much wider for the Cutoff IPW estimator than for the CURE estimator.

We typically expect the ITT estimator to be more conservative than estimators of the causal effect. Although the ITT estimator was in fact more conservative than the causal estimator, the difference is small considering the large proportion of noncompliance. While this may seem counterintuitive, the impact of non-compliance may be different compared to other clinical trials of medication. In the case of medication, we expect a monotone dose-response relationship, and non-compliance with the medication should dilute the treatment effect by reducing the dose received. Here, on the one hand, non-compliant use of high nicotine cigarettes could actually reduce the need for study cigarettes more than the study cigarette itself (e.g., by more effectively alleviating withdrawal). Consequently, one might expect the number of study cigarettes smoked per day to be lower in non-compliant participants than it would be if they were forced to be compliant. On the other hand, non-compliance is also associated with individuals who find VLNC cigarettes particularly unsatisfying. Such individuals might be less inclined to continue to smoke or would smoke less if forced to be compliant.

The results presented here require us to assume that we have correctly modeled the numerator and denominator of the weights and should be interpreted cautiously. Like all models, the assumptions must be considered when interpreting outcomes, and convergent analyses should be used to clarify the likely mechanism whenever possible. Finally, it is important to note that in a regulatory environment in which VLNC cigarettes were the only legally available cigarettes, we would expect that the proportion of smokers using only VLNC cigarettes would be substantially higher than in CENIC-p1, but there would still likely be some use of cigarettes with higher nicotine content (e.g., hoarding, black market).

3.7 Chapter 3 Discussion

Methods for estimating causal effects from randomized clinical trials when there is non-compliance frequently rely on imperfect measures of compliance. Estimators that do not acknowledge the error in the measures of compliance will result in biased estimators of the causal effect. We developed a causal estimator that accounts for uncertainty in compliance status by re-weighting a typical IPCW estimator by a participant's probability of compliance given a biomarker of compliance, the outcome of interest, and confounders. Although we treated the true compliance status as unobserved, we showed the probability of compliance can be estimated by assuming the distribution of the biomarker follows a mixture distribution with separate components for compliers and non-compliers. The simulation demonstrates that our proposed estimator has little bias, good coverage probability, and smaller mean squared error than an *ad hoc* estimator.

The methods developed here have particular relevance to and were motivated by regulatory tobacco research. There is usually substantial noncompliance in regulatory tobacco trials due to the availability of commercial tobacco products. Furthermore, the causal analysis using the methods we have developed, as compared to an ITT analysis, is likely to better estimate the effect we would observe if regulations changing the nicotine composition in cigarettes were enacted. However, our proposed method also has broad applicability for clinical trials conducted in other therapeutic areas. The method is particularly attractive in cases where investigators rely on imperfect measures of compliance, such as participants' self-report (e.g., pill counts, timeline follow back, etc.) because the method explicitly accounts for the uncertainty of compliance status.

The preceding has assumed that either the outcome Y is not subject to measurement or self-report error or that one is interested in the average causal effect on self-reported outcomes. We show in Appendix B that if the observed outcome is subject to measurement error, the proposed approach will estimate the causal effect if there were no measurement error under mild assumptions.

Others have investigated the effect of and possible solutions to mediation estimators when the mediator (e.g., compliance to randomized treatment group) is measured with error (Ogburn and VanderWeele, 2012; Valeri *and others*, 2014). Most prior work has examine the effect on regression-based estimators as opposed to our IPW framework.

Additionally, our approach makes minimal assumptions about measurement error. In particular, we do not need to assume that self-reported compliance (i.e., the covariate measured with error) is a surrogate for true compliance for valid inference. That is, the method does not require that D is conditionally independent of Y given C or that D is conditionally independent of Y given C and X.

There are several limitations to our approach. First, estimating the parameters of the mixture distributions may be computationally challenging, resulting in unstable parameter estimates. In our simulation, we relied on an auxiliary data set that included data from participants whose compliance was known. However, such data sources are frequently available in other settings as well, such as in pharmacokinetic/pharmacodynamic studies. Second, we only considered compliance and outcomes during week 6 of the CENIC-p1 trial. This was done mainly for simplicity, however, and we could develop a longitudinal extension of the estimator, which is a likely subject of future work. Finally, inverse probably weighted estimators are known to be inefficient. The efficiency of the CURE estimator could likely be improved through an augmented weighted estimator (Tsiatis, 2006).

Causal inference methods frequently rely on poor measures of compliance. Our causal estimator weights participants by the product of their probability of compliance given the biomarker of treatment exposure and the inverse probability of compliance given confounders. Our approach suggests that, rather than improving methods of eliciting compliance status from participants, perhaps a more fruitful of area of research is in developing biomarkers of exposure. We restricted our attention to IPCW-like weights and developed the method for a point exposure study, but future work may develop causal estimators in other settings. Our hope is that the proposed methods becomes a standard analysis by investigators estimating causal effects from clinical trials.

Table 3.1: Chapter 3 Simulation Results

n	Estimator	Bias	MC SD	Mean SE	CP	MSE
225	Per Protocol	-0.629	0.173	0.174	0.045	0.426
	Self-Report IPW	-0.403	0.155	0.154	0.257	0.187
	IPW	-0.035	0.330	0.278	0.905	0.110
	Cutoff IPW$_{AUC=0.8}$	-0.140	0.860	0.740	0.978	0.758
	CURE$_{AUC=0.8}$	-0.119	0.768	0.689	0.976	0.603
	Cutoff IPW$_{AUC=0.9}$	-0.037	0.605	0.574	0.972	0.367
	CURE$_{AUC=0.9}$	-0.033	0.523	0.518	0.970	0.274
500	Per Protocol	-0.636	0.114	0.117	0.000	0.417
	Self-Report IPW	-0.405	0.101	0.103	0.024	0.174
	IPW	-0.015	0.209	0.196	0.926	0.044
	Cutoff IPW$_{AUC=0.8}$	-0.010	0.665	0.659	0.983	0.442
	CURE$_{AUC=0.8}$	-0.047	0.530	0.571	0.978	0.283
	Cutoff IPW$_{AUC=0.9}$	0.021	0.368	0.419	0.982	0.136
	CURE$_{AUC=0.9}$	-0.021	0.277	0.344	0.965	0.077
1000	Per Protocol	-0.633	0.086	0.082	0.000	0.408
	Self-Report IPW	-0.405	0.071	0.072	0.000	0.169
	IPW	-0.009	0.154	0.143	0.937	0.024
	Cutoff IPW$_{AUC=0.8}$	0.070	0.480	0.531	0.983	0.235
	CURE$_{AUC=0.8}$	-0.011	0.325	0.418	0.979	0.106
	Cutoff IPW$_{AUC=0.9}$	0.053	0.244	0.279	0.977	0.062
	CURE$_{AUC=0.9}$	-0.007	0.173	0.208	0.963	0.030

Simulation results; MC SD: Monte Carlo standard deviation of the estimator; Mean SE: mean estimated standard error of the estimator; CP: coverage probability of 95% confidence interval; MSE: mean squared error. Subscripts indicate the area under the ROC curve for discriminating compliers from non-compliers.

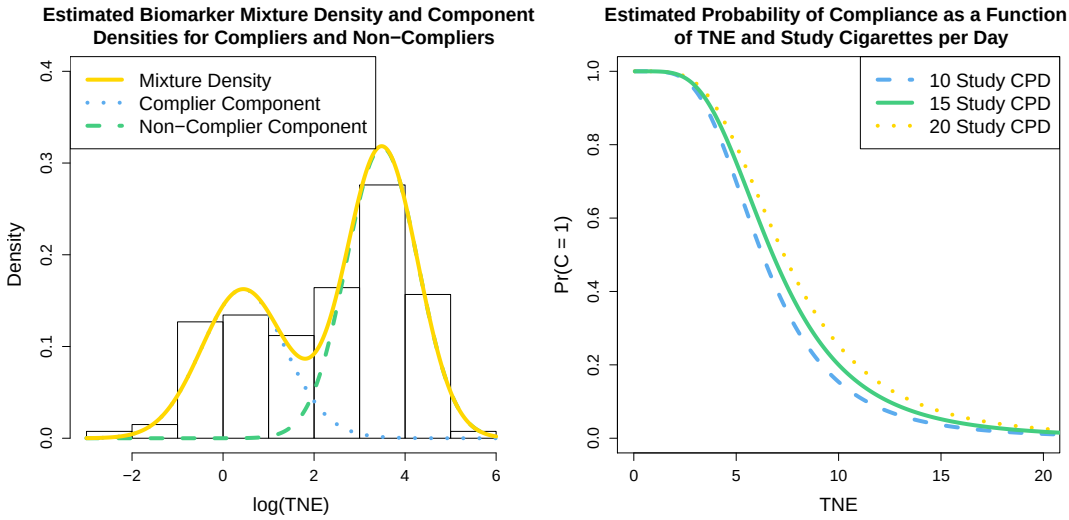

Figure 3.1: Chapter 3 Application Results

Table 3.2: Chapter 3 Application Results

Estimator	$\hat{\mu}(2,0)$	$\hat{\mu}(1,0)$	$\hat{\mu}(2,0) - \hat{\mu}(1,0)$	SE	95% CI
ITT	22.18	15.37	6.81	1.57	(3.78, 10.07)
Causal Estimators					
Per Protocol	22.18	15.12	7.07	1.80	(3.61, 10.63)
Self-Report IPW	22.18	15.19	6.99	1.67	(3.66, 10.38)
Cutoff IPW	22.18	14.83	7.35	3.03	(1.64, 12.99)
CURE	22.18	14.98	7.20	2.79	(2.01, 12.46)

Point estimates, standard error of the estimators, and 95% confidence interval of the estimated causal effect for each estimator. $\mu(2,0)$: mean cigarettes smoked per day for the usual brand group. $\mu(1,0)$: mean cigarettes smoked per day for the VLNC group if all participants were to be compliant.

Chapter 4

Efficiency and Robustness of Causal Effect Estimators When Noncompliance is Measured with Error

4.1 Chapter 4 Introduction

Randomized controlled trials (RCTs) are the gold standard for establishing causation in research. Unfortunately, participant noncompliance to randomized treatment is a common problem in human subject RCTs. This complicates assessing the causal effect of an intervention because, although treatment assignment is randomized, the treatment received is not randomized if subjects are noncompliant.

Intention to treat (ITT) estimators analyze data for all participants according to randomized treatment group regardless of compliance to assigned treatment. Although ITT provides an unbiased estimator of the effect of a treatment as it will be used in practice (Hernán and Hernández-Díaz, 2012), this may be different than the effect that would be observed if all participants were to be compliant, that is, the causal effect of the treatment (Bellamy *and others*, 2007). The causal effect is frequently of significant interest as it may elucidate biological mechanisms or provide investigators and policy

experts an estimated treatment effect if compliance can be increased or enforced.

Estimation of causal effects in the presence of noncompliance is often complicated by the fact that compliance is confounded with other patient characteristics; that is, patient characteristics X are associated with compliance C and with the outcome Y. These characteristics, rather than the treatment effect, may be the cause of observed differences between treatment groups among those observed to be fully compliant.

Several statistical methods have been proposed to estimate the causal effect of treatment in RCTs when subjects may not be fully compliant. Instrumental variable approaches (Angrist *and others*, 1996) estimate causal effects by modeling the effect of an "instrument" (i.e., a variable related to the treatment received but not related to outcome after accounting for treatment received – treatment assignment in this case) on compliance, and adjusting the ITT estimate by the strength of association between the instrument and compliance. As the rate of noncompliance increases, the difference between the ITT estimate and the causal effect will tend to increase (Hernán and Robins, 2006). Another method, principal stratification (Frangakis and Rubin, 2002), estimates causal effects by classifying participants according to joint potential values of post-treatment variables and estimating causal effects within each stratum. For example, in a randomized trial comparing two treatments, we could define one (latent) stratum as participants who would comply if given either treatment A or B. Causal effects are estimated within these latent strata by comparing potential outcomes under the two treatments. This requires modeling assumptions because the potential outcomes are generally known under only one treatment group and because the underlying strata are unknown.

In contrast, inverse probability of compliance weighted (IPCW) estimators (Hernán and Robins, 2006) directly model the probability of compliance given the confounders. Under the assumption of no unmeasured confounders (Robins and Hernán, 2008), and assuming that the model for compliance is correct, the weighted estimator is consistent for the causal effect. Alternatively, if a regression relationship $Y|X, C = 1$ is known, where $C = 1$ indicates compliance, this can be used to estimate the within-group counterfactual mean by averaging fitted values of Y over the observed X for all participants (Lunceford and Davidian, 2004). Augmented estimators combine IPCW and regression estimators by "augmenting" the IPCW estimator with a regression component. When

the regression model is correctly specified, augmented estimators are more efficient than the IPCW estimators. Additionally, these estimators have the appealing property of being doubly-robust: if either the regression model or the model for the probability of compliance is correct, then the estimator is consistent for the causal effect even if the other is misspecified (Tsiatis, 2006).

The methods described above share the common implicit assumption that compliance is measured without error. As we argued in Chapter 3, this is often an unrealistic assumption, particularly when compliance is based on participant self-report. Although Chapter 3 was strongly motivated by an RCT evaluating very low nicotine content cigarettes, investigators often rely on imperfect measures of compliance, such as the number of pills remaining in a bottle returned to the pharmacy in a pharmaceutical trial. Several papers have developed methods to estimate causal mediation effects when the mediator may be measured with error or misclassified (in this context, compliance is a mediator of the effect of assigned treatment and the causal effect of treatment is equivalent to the controlled direct effect) (Ogburn and VanderWeele, 2012; Valeri *and others*, 2014). However, these approaches typically make strong assumptions concerning the measurement error/misclassification mechanism (e.g., surrogacy) which may not reasonable in the context of all RCTs.

To address these limitations, we proposed in Chapter 3 an IPCW-like estimator that, rather than weighting participants according to the inverse of the probability of compliance given the confounders, weights participants according to the product of the probability of compliance given the observed data, including biomarkers of exposure to the treatment, and the inverse of probability of compliance given confounders. Although we treated compliance C as an unobserved variable, we discussed how to estimate the probability of compliance given the observed data by treating the distribution of the biomarker of treatment exposure as a mixture distribution composed of compliers and noncompliers. However, IPCW estimators are known to be highly variable due to instability caused by observations with large weights (Cole and Hernán, 2008). Developing regression-based and augmented IPCW estimators when compliance status is measured with error represent potential approaches to reducing variability, but deriving these estimators is not trivial.

In this work we develop a series of weighted estimators, regression-based estimators,

and an augmented estimator for causal inference in RCTs when compliance is measured with error under minimal assumptions on the measurement error process. Throughout, we assume that we posses a biomarker of treatment exposure that can be used to identify noncompliance. Such biomarkers are often available and can aid in estimation.

The remainder of Chapter 4 proceeds as follows. In Section 4.2, we describe the potential outcomes framework, the observed data, and the assumptions necessary to identify the causal effect. In Section 4.3, we develop weighted estimators, regression-based estimators, and a doubly-robust augmented estimator to estimate causal effects in RCTs when compliance is measured with error. In Section 4.4, we present a simulation study to assess the finite-sample performance of the estimators. We apply the estimators to data from the Center for the Evaluation of Nicotine in Cigarettes, Project 1(CENIC-p1), an RCT of very low nicotine content (VLNC) cigarettes, in Section 4.5, and we conclude in Section 4.6.

4.2 Preliminaries and Notation

4.2.1 Potential Outcomes and Target of Inference

We assume that data are collected from an RCT with treatment groups $A = 1, 2, \ldots, r$. Let Z indicate a measure of compliance without error, with $Z = 0$ indicating compliance and $Z \neq 0$ indicating noncompliance. The precise definition of Z can be tailored to the application. For example, in a pharmaceutical trial, Z may be the number of pills not taken. Define the compliance indicator $C = I(Z = 0)$, and note that we treat both C and Z as unobserved data. Let $Y^*(a, z)$ be the outcome of a randomly-selected participant if, possibly contrary to fact, $A = a$ and $Z = z$. Because for each participant we do not observe all values of $Y^*(a, z)$, $Y^*(a, z)$ is known as a potential outcome. The target of inference is $\mu(a, 0) - \mu(a', 0) = E\{Y^*(a, 0) - Y^*(a', 0)\}$, the mean difference in potential outcomes between treatment groups a and a' if all participants were to be compliant. In the context of mediation literature, $\mu(a, 0) - \mu(a', 0)$ is known as the controlled direct effect (Pearl, 2001), that is, the treatment effect when the mediator, the measure of compliance, is set at the fixed value of 0.

4.2.2 Observed Data

Let Y be the observed outcome for a random participant, let X be a vector of variables associated with C and Y, and let B be a biomarker associated with exposure to treatment A. For example, in pharmaceutical studies B might be the level of drug metabolite in the blood or urine. In the data from the regulatory tobacco trial which motivates our work, B is the level of nicotine in the urine. Let D indicate self-reported compliance, i.e., $D = 1$ if a participant reports compliance, and $D = 0$ if a participant reports any noncompliance. Note that we will introduce estimators that do not rely on D nor on any surrogate of C. However, if self-reported compliance data are available, these data can be incorporated into estimators depending on the scientific question of interest. For example, it may be reasonable to assume that $C = 0$ without error if $D = 0$, that is, we may assume that participants report noncompliance without error as there is usually no social desirability associated with noncompliance. For the remainder of this paper, we will assume that any self-reported measures of compliance are part of the vector X for notational simplicity.

4.2.3 Identifying Assumptions

We make the following standard identifying assumptions (Robins and Hernán, 2008) to relate the observed data to the distribution of the potential outcomes. First, we assume that we have collected sufficient covariates such that compliance is conditionally ignorable. That is, we assume that C is conditionally independent of $Y^*(a, 0)$ given X and A. This is known as the no unmeasured confounders assumption. Second, we assume that for all levels X and A, there is positive probability of compliance, that is $E(C|A, X) > 0$ for all A, X. This is known as the positivity assumption. Finally, we assume that $Y = Y^*(a, 0)$ if $A = a$ and $Z = 0$, that is, if a participant is assigned treatment group a and is compliant, then her observed outcome is the same as it would be if she were forced to be compliant. This is known as the consistency assumption. These assumptions are required assuming either the traditional case where C is observed or in the case we consider where C is unobserved. Further identifying assumptions are required when C is unobserved, and these will be stated where required.

4.3 Causal Estimators

For each causal estimator, we describe estimation of $\mu(a, 0)$, a mean for a single treatment group. Similar estimators can be constructed for $\mu(a', 0)$, and the estimated causal contrast is taken as the difference in estimated means. We present traditional IPCW estimators, regression-based estimators, and an augmented estimator for the case where C is measured without error. For each of these cases, we develop the analogous estimators for the case where C is measured with error, with the goal of making minimal assumptions on measurement error. Rather than developing estimators that rely on a variable measured with error, we take a different approach and treat C as an unobserved variable.

4.3.1 Inverse Probability Weighted Estimators

In the case where C is observed, a traditional IPCW estimator for $\mu(a, 0)$ is the solution to the estimating equation

$$\sum_{i=1}^{n} \frac{I(A_i = a)C_i}{E(C_i|X_i)} \{Y_i - \mu(a, 0)\} = 0.$$

For the case where C is unobserved, we proposed in Chapter 3 estimating $\mu(a, 0)$ by solving the estimating equation

$$\sum_{i=1}^{n} \frac{I(A_i = a)E(C_i|A_i, B_i, X_i, Y_i)}{E(C_i|A_i, X_i)} \{Y_i - \mu(a, 0)\} = 0. \tag{4.1}$$

The estimating function with weights $\frac{E(C|A,B,X,Y)}{E(C|A,X)}$ is similar to the traditional IPCW estimator with weights $\frac{C}{E(C|A,X)}$, but the numerator of the weights is a conditional expectation of C given the observed data rather than an indicator function.

Although C is unobserved, $E(C|A, B, X, Y)$ and $E(C|A, X)$ can be estimated using the observed data. Using Bayes' theorem, we can write $E(C|A = a, B = b, X = x, Y = y)$, the numerator of the weights, as

$$\frac{f(b|a, x, y, c = 1; \xi) \Pr(C = 1|A = a, X = x, Y = y)}{\sum_{j=0}^{1} f(b|a, x, y, c = j; \xi) \Pr(C = j|A = a, X = x, Y = y)} \tag{4.2}$$

where f is the conditional density of B given A, X, Y, and C indexed by parameter vector ξ. The density of $B|A, X, Y$ can be written as a two-component mixture density

$$\begin{aligned} g(b|a,x,y;\xi,\alpha) =& \rho(a,x,y;\alpha)\cdot f(b|a,x,y,c=1;\xi)+ \\ & \{1-\rho(a,x,y;\alpha)\}\cdot f(b|a,x,y,c=0;\xi), \end{aligned} \tag{4.3}$$

where $\rho(a,x,y;\alpha) = \Pr(C=1|A=a,X=x,Y=y;\alpha)$ is indexed by parameter vector α. The parameters for the mixture distribution, ξ and α, can be estimated via maximum likelihood. Thus, although C is unobserved, we can estimate $E(C|A,B,X,Y)$ by substituting estimated parameters of the mixture distribution into (4.2). We refer to the estimator for $\mu(a,0)$ that uses components from the mixture density in (4.3) as the CURE estimator. We showed in Chapter 3 that the CURE estimator is a consistent and asymptotically normal estimator for $\mu(a,0)$, provided that the models for the numerator and denominator of the weights are correctly specified and that the assumptions in Section 4.2.3 are met.

The maximum likelihood estimators of $(\xi^T, \alpha^T)^T$ are the solutions to the score equations

$$\sum_{i=1}^{n} \frac{\partial}{\partial(\xi^T,\alpha^T)^T} \log\{g(B_i|A_i,X_i,Y_i;\xi,\alpha)\} = 0. \tag{4.4}$$

Equation (4.4) may be difficult to solve directly, in which case we can find the maximum likelihood estimates of $(\xi^T, \alpha^T)^T$ using the EM algorithm (Dempster *and others*, 1977).

As an alternative to the factorization of $E(C|A,B,X,Y)$ in (4.2), we can instead write $E(C|A=a,B=b,X=x,Y=y)$ as

$$\frac{f(b|a,x,y,c=1;\xi)h(y|a,x,c=1;\zeta)\Pr(C=1|A=a,X=x)}{\sum_{j=0}^{1} f(b|a,x,y,c=j;\xi)h(y|a,x,c=j;\zeta)\Pr(C=j|A=a,X=x)} \tag{4.5}$$

where h is the conditional density of Y given A, X, and C indexed by parameter vector ζ. This allows us to estimate the joint conditional density of $B, Y|A, X$ as the mixture density

$$\begin{aligned} z(b,y|a,x;\xi,\zeta,\delta) =& \omega(a,x;\delta)f(b|a,x,y,c=1;\xi)h(y|a,x,c=1;\zeta)+ \\ & \{1-\omega(a,x;\delta)\}\cdot f(b|a,x,y,c=0;\xi)h(y|a,x,c=0;\zeta), \end{aligned} \tag{4.6}$$

where $\omega(a,x;\delta) = \Pr(C=1|A=a,X=x;\delta)$ is indexed by parameter vector δ. We refer to the estimator for $\mu(a,0)$ that uses components from the mixture density in

(4.6) as the CURE+ estimator. Similar to the CURE estimator, the CURE+ estimator is consistent assuming that the models for the density in (4.6) are correct and the assumptions in Section 4.2.3 are met.

The maximum likelihood estimates of $(\xi^T, \zeta^T, \delta^T)^T$ are the solutions to the score equations

$$\sum_{i=1}^{n} \frac{\partial}{\partial(\xi^T, \zeta^T, \delta^T)^T} z(B_i, Y_i | A_i, X_i; \xi, \zeta, \delta) = 0 \tag{4.7}$$

As in Equation (4.4), Equation (4.7) may be difficult to solve directly, and the maximum likelihood estimates of $(\xi^T, \zeta^T, \delta^T)^T$ can be found with the EM algorithm.

We note that unlike the CURE estimator, the CURE+ estimator requires specifying the conditional distribution of Y given A, X, C. The advantage of having to specify $h(y|a, x, c; \zeta)$ is that this may lead to greater separation between the compliers and non-compliers, allowing for easier identification of the maximum likelihood estimates using the EM algorithm. Additional advantages of this approach will become apparent in Section 4.3.2.

In most applications, the denominator of the weights is unknown and must be estimated. Because the denominator is between 0 and 1, we specify a regression model $E(C|A, X) = \pi(A, X; \beta) = g^{-1}\left\{\beta_0 + X^T\beta_1 + I(A = 2)\beta_2 + \cdots + I(A = r)\beta_r\right\}$, where g is a link function that maps from (0, 1) to $\mathbb{R}$, such as the logit or probit link, and $\beta = (\beta_0, \beta_1^T, \beta_2, \ldots, \beta_r)^T$ is a vector of unknown regression coefficients. We can estimate β by solving the score equations

$$\sum_{i=1}^{n} \frac{E(C_i|A_i, B_i, X_i, Y_i) - \pi_i(A_i, X_i; \beta)}{\pi_i(A_i, X_i; \beta)\left\{1 - \pi_i(A_i, X_i; \beta)\right\}} \frac{\partial \pi_i(A_i, X_i; \beta)}{\partial \beta^T} = 0 \tag{4.8}$$

That is, $E(C|A, B, X, Y)$ is the "response" of the regression model for $E(C|A, X)$. Note that we can estimate β simultaneously with either $(\xi^T, \alpha^T)^T$ or $(\xi^T, \zeta^T, \delta^T)^T$ by stacking Equation (4.8) with Equation (4.4) or (4.7), respectively. This is equivalent to replacing $E(C|A, X, B, Y)$ in Equation (4.8) with the estimated expectation $E\left(C|A, B, X, Y; \hat{\xi}_n, \hat{\alpha}_n\right)$ or $E\left(C|A, B, X, Y; \hat{\xi}_n, \hat{\zeta}_n, \hat{\delta}_n\right)$, where $\hat{\xi}_n, \hat{\alpha}_n, \hat{\zeta}_n$, and $\hat{\delta}_n$ are the estimates of ξ, α, ζ, and δ.

4.3.2 Regression-Based Estimators

In the case where C is observed, as an alternative to IPCW estimation, we can instead estimate $\mu(a,0)$ by solving the estimating equation

$$\sum_{i=1}^{n} \{\eta(A=a, X_i;\gamma) - \mu(a,0)\} = 0. \tag{4.9}$$

where $\eta(A, X;\gamma) = E(Y|A, X, C=1)$ and γ is a vector of regression coefficients. This is referred to as a regression-based estimator because, prior to solving Equation (4.9), the conditional mean model for the outcome $\eta(A, X;\gamma)$ must be specified. For example, we can assume the mean model $\eta(A, X;\gamma) = \gamma_0 + X^T\gamma_1 + I(A=2)\gamma_2 + \cdots + I(A=r)\gamma_r$, but other paramaterizations are possible. In the case where C is observed, one can estimate the vector of regression coefficients γ by solving the estimating equation

$$\sum_{i=1}^{n} C_i \{Y_i - \eta(A_i, X_i;\gamma)\} \frac{\partial \eta(A_i, X_i;\gamma)}{\partial \gamma^T} = 0 \tag{4.10}$$

To estimate $\mu(a,0)$, Equations (4.9) and (4.10) can be solved jointly, which is equivalent to replacing $\eta(A=a, X;\gamma)$ in Equation (4.9) with $\eta(A=a, X;\hat{\gamma}_n)$.

Assuming that the model for $E(Y|A, X, C=1)$ is correct, regression-based estimators are consistent estimators for $\mu(a,0)$ and have smaller asymptotic variance than IPCW estimators (Lunceford and Davidian, 2004). Note that regression-based estimators have a potential advantage over IPCW estimators in that they do not require specifying a model for $E(C|A, X)$, and, unlike IPCW, they do not assign weights of 0 to some participants when estimating $\mu(a,0)$, but this comes at the cost of needing to correctly specify a model for $E(Y|A, X, C=1)$. See Lunceford and Davidian (2004) for further discussion of advantages and disadvantages of weighted estimators compared to regression-based estimators.

In the case where C is unobserved, both specifications of the mixture distributions in Equations (4.3) and (4.6) offer a means of using $E(C|A, B, X, Y)$ to estimate $E(Y|A, X, C=1)$, which can then be used in Equation (4.9). Using $E(C|A, B, X, Y)$, we can estimate the regression coefficients γ by solving the estimating equations

$$\sum_{i=1}^{n} E(C_i|A_i, B_i, X_i, Y_i) \{Y_i - \eta(A_i, X_i;\gamma)\} \frac{\partial \eta(A_i, X_i;\gamma)}{\partial \gamma^T} = 0. \tag{4.11}$$

In expectation, weighting by $E(C|A,B,X,Y)$ is equivalent to the estimating function in Equation (4.10). By iterated expectation,

$$\sum_{i=1}^{n} E\left[E(C_i|A_i,B_i,X_i,Y_i)\left\{Y_i-\eta(A_i,X_i;\gamma)\right\}\frac{\partial\eta(A_i,X_i;\gamma)}{\partial\gamma^T}\right]$$
$$=\sum_{i=1}^{n} E\left[C_i\left\{Y_i-\eta(A_i,X_i;\gamma)\right\}\frac{\partial\eta(A_i,X_i;\gamma)}{\partial\gamma^T}\right]=0.$$

Therefore, under suitable regularity conditions, we can obtain a consistent and asymptotically normal estimator for γ and $\mu(a,0)$ provided that we can obtain a consistent estimator of $E(C|A,B,X,Y)$.

As discussed in Section 4.3.1, $E(C|A,B,X,Y)$ can be estimated directly from mixture components of the mixture density in (4.3). Thus we can consistently estimate $\mu(a,0)$ by jointly solving Equations (4.4), (4.9), and (4.11). Because this estimator uses a weighted regression model, we refer to $\hat{\mu}(a,0)$, given by the solution to these estimating equations, as the W-REG estimator. To be explicit, to obtain consistent estimation of $\mu(a,0)$, W-REG requires correctly specifying each of the components of the mixture distribution in (4.3) (i.e., $\Pr(C|A=a,X=x,Y=y;\alpha)$ and the distribution of $B|A,X,Y,C$) as well as the model for the conditional mean of $Y|A,X,C=1$.

Note that, by estimating the parameters in Equation (4.6), we will already have estimated the regression coefficients of the conditional mean model of $Y|A,X,C=1$ (i.e., γ). Thus, we can simply estimate $\mu(a,0)$ by jointly solving the estimating Equations (4.7) and (4.9), which is equivalent to replacing $\eta\left(A=a,X;\gamma\right)$ in Equation (4.9) with $\eta\left(A=a,X;\hat{\gamma}_n\right)$. Because this estimator uses a regression model with coefficients estimated from the mixture distribution using an EM algorithm, we refer to this estimator as the EM-REG estimator. To be clear, EM-REG requires that the analyst correctly specify all the components of the mixture distribution in (4.6) (i.e., $\Pr(C=1|A=a,X=x;\alpha)$ and the distributions of $B|A,X,Y,C$ and $Y|A,X,C$).

W-REG has one potential advantage over EM-REG. The EM-REG estimator requires that the analyst specify a model for $E(Y|A,X,C=1)$ prior to fitting the mixture distribution, whereas W-REG first allows estimation of the biomarker mixture distribution without specifying a model for $E(Y|A,X,C=1)$. Because fitting mixture distributions can be computationally demanding, fitting several models for $E(Y|A,X,C=1)$

as part of the mixture distribution and assessing model fit may be challenging. In contrast, once the weights $E\left(C|A, X, B, Y; \hat{\xi}_n, \hat{\alpha}_n\right)$ for W-REG have been estimated, the analyst can easily fit multiple models and proceed using standard model checking and diagnostics for $E(Y|A, X, C = 1)$.

4.3.3 Augmented Estimators

Augmented estimators incorporate both weighted estimators and regression-based estimators. In the case where C is observed, an augmented estimator for $\mu(a,0)$ is the solution to the estimating equation

$$\sum_{i=1}^{n} I(A_i = a)\left[\frac{C_i Y_i}{E(C_i|A_i,X_i)} - \frac{\{C_i - E(C_i|A_i,X_i)\}\,\eta(A=a,X_i;\gamma)}{E(C_i|A_i,X_i)} - \mu(a,0)\right] = 0. \tag{4.12}$$

This is similar to the IPCW estimator, but it is "augmented" with the term $\frac{\{C-E(C|A,X)\}\eta(A=a,X;\gamma)}{E(C|A,X)}$ which uses the regression function $\eta(A=a,X;\gamma)$. If the conditional regression model $\eta(A=a,X;\gamma)$ is correctly specified, augmented estimators gain efficiency over IPCW estimators. Additionally, assuming C is observed, the estimator for $\mu(a,0)$ given by the solution to (4.12) is consistent when either the model for $E(C|A,X)$ is correctly specified or when the model for $E(Y|A,X,C=1) = \eta(A,X;\gamma)$ is correctly specified even if the other model is misspecified (Lunceford and Davidian, 2004). Thus, augmented estimators are said to be doubly-robust.

In the case where C is unobserved, an augmented estimator for $\mu(a,0)$ is the solution to the estimating equation

$$\sum_{i=1}^{n} I(A_i = a)\left[\frac{E(C_i|A_i,B_i,X_i,Y_i)Y_i}{E(C_i|A_i,X_i)} - \frac{\{E(C_i|A_i,B_i,X_i,Y_i) - E(C_i|A_i,X_i)\}\,\eta(A=a,X_i;\gamma)}{E(C_i|A_i,X_i)} - \mu(a,0)\right] = 0.$$

This is similar to the estimating equation in (4.12), but we have replaced C, the indicator variable of compliance, with the conditional expectation $E(C|A,B,X,Y)$. Because this is an augmented CURE estimator, we refer to it as the A-CURE estimator.

For ease of exposition, we assume for the remainder of this section only a single treatment group with A = 1 for all participants, but the results easily generalize. The A-CURE estimator

$$\hat{\mu}_n(1,0) = \frac{1}{n}\sum_{i=1}^{n} \frac{E\left(C_i|B_i,X_i,Y_i;\hat{\xi}_n,\hat{\alpha}_n\right)Y_i}{E\left(C_i|X_i;\hat{\beta}_n\right)} - \frac{\left\{E\left(C_i|B_i,X_i,Y_i;\hat{\xi}_n,\hat{\alpha}_n\right) - E\left(C_i|X_i;\hat{\beta}_n\right)\right\}\eta\left(A=1,X_i;\hat{\gamma}_n\right)}{E\left(C_i|X_i;\hat{\beta}_n\right)}$$

is a consistent estimator for $\mu(1,0)$ provided that the model for $E(C|B,X,Y)$ is correctly specified, and either the model for $E(C|X)$ or the model for $E(Y|X,C=1)$ is correctly specified. That is, if the model for $E(C|B,X,Y)$ is correct, then $\hat{\mu}_n(1,0)$ is a doubly-robust estimator for $\mu(1,0)$.

To show this, we take the approach in Tsiatis (2006) and use the conventions $\hat{\xi}_n \xrightarrow{P} \xi^*$, $\hat{\alpha}_n \xrightarrow{P} \alpha^*$, $\hat{\beta}_n \xrightarrow{P} \beta^*$, and $\hat{\gamma}_n \xrightarrow{P} \gamma^*$ to denote convergence in probability whether or not the models are correct (i.e., ξ^* is the" least wrong" parameter if the model is misspecified and similarly for α^*, β^*, and γ^*) . If the model is correctly specified, then $\xi^* = \xi_0, \alpha^* = \alpha_0, \beta^* = \beta_0$, and $\gamma^* = \gamma_0$, that is, the subscript 0 indicates the true parameter values for the correct models. Because $\hat{\mu}_n(1,0)$ is a sample mean, under suitable regularity conditions it converges in probability to

$$E\left[\frac{E\left(C|B,X,Y;\xi^*,\alpha^*\right)Y}{E\left(C|X;\beta^*\right)} - \frac{\left\{E\left(C|B,X,Y;\xi^*,\alpha^*\right) - E\left(C|X;\beta^*\right)\right\}\eta\left(A=1,X;\gamma^*\right)}{E\left(C|X;\beta^*\right)}\right].$$

When $\xi^* = \xi_0$ and $\alpha^* = \alpha_0$, that is, when the models for the parameters of the mixture density (4.3) are correct, $\hat{\mu}_n(1,0)$ converges in probability to

$$\begin{aligned} &E\left[\frac{E\left(C|B,X,Y;\xi_0,\alpha_0\right)Y}{E\left(C|X;\beta^*\right)} - \frac{\left\{E\left(C|B,X,Y;\xi_0,\alpha_0\right) - E\left(C|X;\beta^*\right)\right\}\eta\left(A=1,X;\gamma^*\right)}{E\left(C|X;\beta^*\right)}\right] \\ &= E\left[\frac{CY}{E\left(C|X;\beta^*\right)} - \frac{\left\{C - E\left(C|X;\beta^*\right)\right\}\eta\left(A=1,X;\gamma^*\right)}{E\left(C|X;\beta^*\right)}\right] \end{aligned} \tag{4.13}$$

The equality follows from iterated expectation. By the consistency assumption,

$$\frac{CY}{E(C|X;\beta^*)} = \frac{CY^*(1,0)}{E(C|X;\beta^*)} = Y^*(1,0) + \frac{\left\{C - E(C|X;\beta^*)\right\}Y^*(1,0)}{E(C|X;\beta^*)}. \tag{4.14}$$

Substituting (4.14) into (4.13), we can write (4.13) as

$$E\left\{Y^*(1,0)\right\} + E\left[\frac{\left\{C - E(C|X;\beta^*)\right\}\left\{Y^*(1,0) - \eta(A=1,X;\gamma^*)\right\}}{E(C|X;\beta^*)}\right]. \tag{4.15}$$

Because the first term in (4.15) is equal to $\mu(1,0)$, $\hat{\mu}_n(1,0)$ is doubly-robust provided that the second term in (4.15) equals 0. The second term equals 0 when either $\beta^* = \beta_0$ or $\gamma^* = \gamma_0$, that is, when either the model for $E(C|X;\beta)$ is

correct or when the model for $E(Y|X, C = 1; \gamma) = \eta(A = 1, X; \gamma)$ is correct. As in Tsiatis (2006), we will show this by taking iterated expectations.

First, assume that the model for $E(C|X, \beta)$ is correct, that is, $\beta^* = \beta_0$. By an iterated expectation conditioning on $Y^*(1,0)$ and X, the second term in (4.15) equals

$$E\left(\frac{[E\{C|X, Y^*(1,0)\} - E(C|X;\beta_0)]\{Y^*(1,0) - \eta(A=1,X;\gamma^*)\}}{E(C|X;\beta_0)}\right)$$
$$= E\left[\frac{\{E(C|X) - E(C|X;\beta_0)\}\{Y^*(1,0) - \eta(A=1,X;\gamma^*)\}}{E(C|X;\beta_0)}\right] = 0,$$

where the first equality follows from the assumption of no unmeasured confounding. Thus we conclude that $\hat{\mu}_n(1,0)$ is a consistent estimator for $\mu(1,0)$ if $\beta^* = \beta_0$.

Now assume that the model $E(Y|C = 1, X; \gamma)$ is correctly specified, that is, $\gamma^* = \gamma_0$. By an iterated expectation conditioning on C and X, the second term in (4.15) equals

$$E\left[\frac{\{C - E(C|X;\beta^*)\}\{E\{Y^*(1,0)|C,X\} - \eta(A=1,X;\gamma_0)\}}{E(C|X;\beta^*)}\right]. \tag{4.16}$$

By the assumption of no unmeasured confounding, $E\{Y^*(1,0)|C,X\} = E\{Y^*(1,0)|C=1,X\} = \eta(A=1,X;\gamma_0)$. Thus we conclude that $\hat{\mu}_n(1,0)$ is a consistent estimator for $\mu(1,0)$ if $\gamma^* = \gamma_0$. Hence, $\hat{\mu}_n(1,0)$ is a doubly-robust estimator for $\mu(1,0)$.

Note that an augmented estimator based on estimating $E(C|B,X,Y)$ using the mixture density (4.6) is less useful. In Equation (4.6), one must correctly specify a model for $Y|X,C$ *a priori* in order to consistently estimate $E(C|B,X,Y)$. That is, an augmented estimator based on estimating $E(C|B,X,Y)$ using components of the mixture density (4.6) would not be doubly robust.

The A-CURE estimator is attractive compared to the regression-based estimators. For consistent estimation of $\mu(1,0)$, the A-CURE and regression-based estimators all rely on the assumption that the distribution of $B|A,X,Y$ has

been correctly specified, but the regression-based estimators further require that $E(Y|A, X, C = 1)$ is correctly specified. In contrast, the A-CURE estimator is still consistent provided that *either* the mean model for $E(Y|A, X, C = 1)$ is correct *or* that the model for $E(C|A, X)$ is correct, essentially giving the analyst two chances to be correct instead of just one.

4.3.4 Overview

In Table 4.1 we summarize the quantities that must be correctly specified and estimated in order to achieve consistent and asymptotically normal estimators of $\mu(a,0)$ for each estimator. We also indicate which estimators will be consistent under misspecification of $h(Y|X,C)$ (the conditional distribution of Y given X and C) or $E(Y|X,C)$. For comparison, we also include the quantities that must be correctly specified to achieve consistency in "traditional" IPCW, regression, and augmented IPCW estimators when the compliance status is observed.

All estimators for $\mu(a,0)$ will be consistent and asymptotically normal if the components in Table 4.1 are correctly specified. Let $\mathbf{Z}_i = (A_i, B_i, X_i, Y_i)$ be the observed data for the ith participant. Define $\psi_i\{\mathbf{Z}_i; \mu(a,0), \lambda\}$ to be the mutli-dimensional estimating function from stacking the estimating functions for $\mu(a,0)$ and any other nuisance parameters that must be estimated. For example, for the CURE estimator, λ would include $\lambda = (\xi^T, \alpha^T, \beta^T)^T$ and ψ would include Equations (4.1), (4.4), and (4.8). Under suitable regularity conditions,

$$\sqrt{n}\left[\left\{\hat{\mu}(a,0), \hat{\lambda}^T\right\}^T - \left\{\mu(a,0), \lambda^T\right\}^T\right] \xrightarrow{D} N\left(0, U^{-1}V(U^{-1})^T\right),$$

where $V = E([\psi_i\{\mathbf{Z}_i; \mu(a,0), \lambda\}][\psi_i\{\mathbf{Z_i}; \mu(a,0), \lambda, \}]^T)$ and $U = -E\left[\frac{\partial \psi_i\{\mathbf{Z}_i; \mu(a,0), \lambda\}}{\partial\{\mu(a,0), \lambda^T\}^T}\right]$. The sandwich covariance matrix $U^{-1}V(U^{-1})^T$ can be estimated using the empirical averages for U and V (see, for example, Stefanski and Boos (2002)) or with the bootstrap.

4.4 Simulation

We conducted a simulation study to characterize the finite-sample performance of the estimators described in Section 4.3. For simplicity, we considered a scenario with only a single treatment group with $A = 1$ for all participants. We give special attention to the cases where the conditional mean of Y given $X, C = 1$ is either specified correctly or are misspecified.

To facilitate data generation, define the latent continuous measure of compliance C'. We generated (C', X_1, X_2) from a multivariate normal distribution with mean vector

$(0, 2, 2)^T$ and covariance matrix $\begin{pmatrix} 1.000 & 0.200 & 0.075 \\ 0.200 & 1.000 & 0.200 \\ 0.075 & 0.200 & 1.000 \end{pmatrix}$. Using this covariance matrix, X_1 is more strongly associated with C' than is X_2, and hence X_1 is more strongly associated with compliance. We defined the compliance indicator $C = I\left\{C' > \Phi^{-1}(0.8)\right\}$, where Φ is the standard normal distribution function. This gives $\Pr(C = 1) = 0.20$, roughly the estimated probability of compliance in the application we consider in Section 4.5. We simulated the outcome as $Y|X_1, X_2, C \sim N\left(5 - 2.25C + X_1 + X_2 + \nu X_3, 1.25^2\right)$, where $X_3 = X_1X_2$ for a model with an interaction and $X_3 = X_1^2$ for a model with a quadratic term, and where ν was equal to 0, 1, or 2. The biomarker B was generated as $B|Y, C \sim N\left(-9.3 - 0.8C + 0.7Y, 0.40^2\right)$. Our data generating mechanism implies that B and X are conditionally independent given C, and Y. Although this assumption is not required, it simplifies the simulation scenario, because in the correctly specified conditional mean function of B in the mixture densities in (4.3) and (4.6), coefficients for X_1 and X_2 are 0 and thus do not need to be estimated. As in Chapter 3, we included participants comprising 10% of the sample who were known to be compliant, that is, $C = 1$ without error. Data for known compliers was generated as described above, but, rather than randomly generating C, we set $C = 1$ for these subjects. Known compliers contributed to estimation of mixture distributions as follows. For known compliers, let $K = 1$, and let $K = 0$ for all other subjects. Let n_k denote the number of known compliers, and let $m = n + n_k$. To include known compliers in estimation of the mixture distributions, we solved the modified score equations

$$\sum_{i=1}^{m} \frac{\partial}{\partial(\xi^T, \alpha^T)^T} \{(1 - K_i) \cdot \log g(B_i|X_i, Y_i; \xi, \alpha) \\ K_i \cdot \log f(B_i|X_i, Y_i, c = 1; \xi)\} = 0$$

in place of the score equations (4.4), and

$$\sum_{i=1}^{m} \frac{\partial}{\partial(\xi^T, \zeta^T, \delta^T)^T} \{(1 - K_i) \cdot \log z(B_i, Y_i|X_i; \xi, \zeta, \delta) \\ K_i \cdot \log f(B_i|X_i, Y_i, c = 1; \xi)\} = 0$$

in place of the score equations (4.7). That is, known compliers contribute to estimation

of the mixture distributions only through the information they contain about the conditional density of B. They make no other contributions to estimation of $\mu(1,0)$. We considered sample sizes of 275, 550, and 1,100, including the known compliers. 1,000 Monte Carlo datasets were generated for each scenario.

We compared 8 estimators of $\hat{\mu}(1,0)$: the 5 estimators described in Section 4.3 and three traditional estimators that assume C is known without error: 1) an IPW estimator with weights equal to $\frac{C}{E(C|X)}$, a regression-based estimator (REG) that estimates the linear model $Y|X, C=1$ and solves the estimating equation $\sum_{i=1}^{n}\{E(Y_i|X_i, C=1) - \mu(1,0)\}$, and 3) an augmented IPW estimator (A-IPW) that combines the IPW and REG estimators. Although C is treated as an unobserved variable in our case, we included these 3 estimators to illustrate the consequences of relying on imperfect measures of compliance.

For all models that require estimation of a mixture distribution to estimate $E(C|B, X, Y)$, we assumed a linear regression model with normally distributed errors for $B|Y, C$. For the CURE estimator, we estimated $E(C|X, Y)$ using a generalized linear model (GLM) with logit link. Note that for the CURE estimator, this GLM is not exactly concordant with the data generating mechanism, but it is simple, easy to implement, and achieves reasonable small-sample performance. For the CURE+ estimator, we assumed a linear regression model for $Y|X, C$ with normally distributed errors, and we estimated $E(C|X)$ using a GLM with probit link. For the EM-REG estimator, we used the estimated model for $Y|X, C$ to solve the estimating equation given in Equation (4.9). For the W-REG estimator, we used the estimated expectation $E(C|B, X, Y)$ to solve Equation (4.11) and used the coefficient estimates to solve Equation (4.9). For the A-CURE estimator, we obtained estimates of the necessary components using the same approach as in the CURE and W-REG estimators.

In this simulation we considered the consequence of misspecifying the conditional distribution of $Y|X, C$. Specifically, we considered the effect of omitting terms for X_3 when $\nu \neq 0$. Note that the CURE estimator is never misspecified in these scenarios because the estimator does not require estimation of the conditional distribution of Y. Because all models require a correctly specified model for $B|Y, X, C$, we only consider scenarios where the model for $B|Y, X, C$ is correctly specified.

For each model requiring estimation via the EM algorithm, we tried 4 sets of starting

values, and we chose the model that gave the lowest negative log likelihood. The first set of starting values used parameters and coefficients estimated from models using the actual compliance C. The second set of starting values were the true values of the parameters and coefficients; for misspecified models, these were found by estimating parameters and coefficients from misspecified models using a very large sample. The remaining sets of starting values were generated from the first set of starting values as follows. For a coefficient or parameter D from the first set, the new starting value was $D + D \times U$, where U is a uniform random variable on the interval (-0.35, 0.35).

Scenarios in which the model for $Y|X, C$ is misspecified occasionally resulted in estimates of $\mu(1, 0)$ which were clearly outliers in the sampling distribution. In practice, investigators are likely to fit a variety of causal models to seek converging lines of evidence of the magnitude of a causal effect. Thus, outliers are generally easily identified and omitted in practice, and we feel interpretation of simulation results may be more meaningful with outliers removed. We present results with outliers excluded or included. To remove outliers, for each estimator within each scenario, we defined upper and lower limits as the median $\pm 9/4\times$ IQR (interquartile range; $9/4\times$ IQR is roughly 3 standard deviations for a normally distributed random variable). For results excluding outliers, for each estimator the estimates falling below the lower limit or above the upper limit were excluded.

Tables 4.2, 4.3, and 4.4 provide results when the regression model for the outcome given confounders X and compliance C is correctly specified. All estimators show a small amount of bias that is attenuated with increasing sample size. Among the "gold standard" estimators which use the true compliance status, all were more efficient than the proposed estimators that do not use the true compliance status. Across the scenarios presented in tables 4.2, 4.3, and 4.4, the "gold standard" regression estimator was substantially more efficient than the IPW estimator (the ratio of REG MSE to IPW MSE ranged from 0.775 to 0.924). However, as expected, the augmented IPW estimator recovers nearly all the difference in efficiency between IPW and REG.

Considering the estimators that do not use the true compliance status, CURE+ was much more efficient than CURE when the true outcome model was correctly specified. Using more data (i.e., the outcome) may more efficiently identify the components of the mixture distribution leading to more efficient estimation of $E(C|A, B, X, Y)$. As

is the case for "gold standard" estimators, regression-based estimators were generally more efficient when the outcome model is correctly specified. EM-REG, which uses a maximum likelihood estimator for the parameters of the outcome model, was generally more efficient than W-REG. Augmenting the CURE estimator (i.e., A-CURE) improves the efficiency with MSEs generally comparable to the W-REG estimator.

Tables 4.5 and 4.6 show the results when the coefficient for the interaction and quadratic terms are non-zero but the model is misspecified, that is, the regression model for the outcome omits the interaction or quadratic term. For the interaction model, CURE performs well because there is no model misspecification for this estimator. CURE+ shows bias that is only weakly attenuated with increasing sample size. The EM-REG and W-REG estimators have small bias when the interaction coefficient equals 1, but the magnitude of bias increases substantially for a stronger interaction. For the quadratic models with misspecification, the bias of the CURE+, EM-REG, and W-REG estimators is more substantial than for the interaction. The differences in the performance of these estimators is explained by noting that the quadratic models include a quadratic term for X_1, and, because X_1 is more strongly associated with compliance than X_2, the models with misspecification of $E(Y|X, C = 1)$ tend to perform worse under the quadratic model than under the interaction model. The A-CURE estimator has bias commensurate with the CURE estimator, but the MSE of the A-CURE estimator is now higher than the MSE of the CURE estimator. This is consistent with the performance of the "gold standard" estimators in which the AIPW estimator was less efficient than the IPW estimator when the outcome regression model was misspecified. Tables 4.10 and 4.11 show the results when the interaction and quadratic models are misspecified with outliers included.

Here we give some intuition for why the CURE+ and EM-REG estimators have a large number of outliers and very large bias for some cases. We consider the Monte Carlo iteration that gave the largest magnitude of bias for the CURE+ estimator for $n = 1,100$ under the misspecified quadratic model with coefficient $\nu = 2$. Figure 4.4 shows the estimated values of $E(C|B, X, Y)$ (the numerator of the CURE+ weights) as a function of X_1. Several things are noteworthy by about this figure. First, the average value of the estimated values of $E(C|B, X, Y)$ in the sample (i.e., an estimator of $E(C)$) is very close 0. Second, there is high separation of $E(C|B, X, Y)$ as a function of X_1,

so attempting to fit a probit model with these data results in very large magnitude coefficients with some fitted probabilities close to 0 or equal to 0, so the weights can become very unstable. Third, the marginal distribution of X_1 is $N(2,1)$, so a value of $X_1 \approx 6$ is clearly an outlier, and given the large quadratic coefficient, this individual will have a very large value of Y. Under misspecified models, it appears that the model fitting in the EM algorithm favors labeling a single outlying individual as compliant and all others as non-compliant. Given that this is the only individual with $E(C|B,X,Y) \approx 1$, this individual's outcome has a large impact on the estimator. Informal examination of other iterations with a high values of error had similar problems. The EM-REG estimator will have similar problems as the estimated model for $E(Y|X,C=1)$ is essentially based on a single individual.

In Appendix C.1, we show analogous results for simulations that do not include participants who are known to be compliant. In general, the performance of the estimators is similar to the case where known compliers are included.

4.5 Application to CENIC-p1 Data

We applied the 5 estimators described in Section 4.3 to data from CENIC-p1 to estimate the causal effect of VLNC cigarettes on the number of cigarettes smoked per day during week 6 of the trial. CENIC-p1 included seven treatment groups: a usual brand control condition and six experimental conditions with nicotine content ranging from 15.8 mg/g of tobacco to 0.4 mg/g of tobacco. In addition, one condition had 0.4 mg/g of tobacco and high tar to evaluate the impact of tar yield on the effect of nicotine reduction. For the purposes of this illustration, we focus on the contrast between the two VLNC conditions (i.e. 0.4 mg/g and the 0.4 mg/g, high tar conditions, combined) versus the usual brand control condition. As in Chapter 3, we only considered compliance and outcomes during week 6 of the trial. We let $A = 1$ if the participant was assigned to smoke VLNC cigarettes ($n = 242$), and $A = 2$ if the participant was assigned to smoke usual brand cigarettes ($n = 118$). In this study, subjects are considered noncompliant if they smoke cigarettes which are not provided as part of the study (i.e., commercial or "non-study" cigarettes).

The goal of the analysis was to estimate $\mu(2,0) - \mu(1,0)$, the expected reduction in

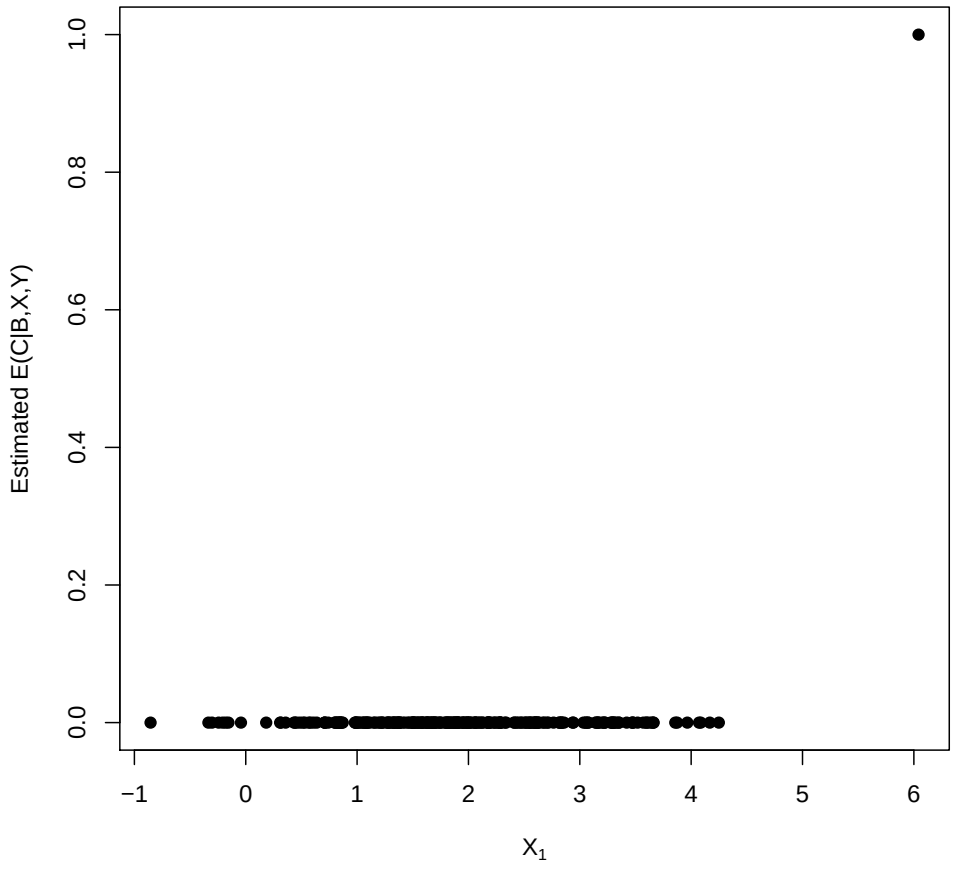

Figure 4.1: Estimated $E(C|B, X, Y)$ as a function of X_1 for the CURE+ estimator with the largest error for $n = 1,100$, misspecified model with quadratic coefficient of 2

cigarettes smoked per day during week 6 if smoking only VLNC cigarettes. Because the usual brand group is meant to represent smoking of commercial cigarettes, all participants in this group were treated as compliant even if they reported smoking non-study cigarettes (i.e., cigarettes that were not provided by trial personnel). Thus, $\mu(2, 0)$ is the sample average of the number of cigarettes smoked per day for this group.

For the CURE and CURE+ estimators, we estimated the probability of compliance following the approach in Section 4.3.1 using the (natural) logarithm of total nicotine

equivalent (TNE) measured at week 6 as the biomarker B. In fitting the mixture distributions in Equations (4.3) and (4.6), we assumed a linear regression models for $B|Y, C$ with normally distributed errors and no shared parameters between different levels of C. As in the simulation, we assumed that B and X are conditionally independent given C and Y. As described in (Denlinger *and others*, 2016), CENIC-p1 also included an auxiliary study that included data from 23 smokers who volunteered to be sequestered in a hotel for 4 nights with access to only VLNC cigarettes. These participants are known to be compliant, and we incorporated B and Y from these individuals to assist in estimation of the mixture densities. Chapter 3 describes in detail how data for these participants can be incorporated. Briefly, these individuals contribute data to the likelihood for the distribution of $B|Y, C = 1$, but they make no other contributions to estimation (i.e., their outcomes are not used to estimate the causal effect, and their covariates X are not used in any way). We assumed logistic regression models for $\Pr(C = 1|X, Y)$ and $\Pr(C = 1|X)$ of Equations (4.3) and (4.6), where the confounders X included age, level of addiction (baseline cigarettes per day and log of TNE), measures of withdrawal (Minnesota Nicotine Withdrawal Scale at week 5 and maximum acute withdrawal), and satisfaction with and craving for VLNC (Cigarette Evaluation Scale and Questionnaire of Smoking Urges at week 5) and normal nicotine cigarettes (Questionnaire of Smoking Urges at Week 5). For the distribution of $Y|X, C$, we assumed linear regression models with linear terms for all X, with normally distributed errors and no shared parameters between different levels of C. As in Chapter 3, we assumed that individuals with $A = 1$ who self-reported any noncompliance (that is, $D = 0$ using Chapter 3 notation) reported noncompliance without error, and we let $\Pr(C = 1|X, Y) = 0$ for these individuals. As a result, these individuals did not contribute to estimation of the mixture distribution. For both the CURE and CURE+ estimators, we assumed a logistic model for $E(C|X)$ using X as described above. For the EM-REG estimator, we used the estimated model for $Y|X, C$ to solve the estimating equation given in Equation (4.9). For the W-REG estimator, we used the estimated expectation $E(C|B, X, Y)$ to solve Equation (4.11) and used the coefficient estimates to solve Equation (4.9). For the A-CURE estimator, we combined the CURE and W-REG estimators. We used the bootstrap percentile method with 1,000 bootstrap re-sampled data sets to compute 95% confidence intervals. In Section C.2 of Appendix C we show

point estimates and 95% CIs for all all components required to implement the various causal estimators.

Table 4.12 shows the estimated causal effect of VLNC cigarettes on number of cigarettes smoked per day. The CURE estimator gives the most optimistic estimate of the causal effect. The W-REG and A-CURE estimators give similar estimates and are close to the ITT estimate. The CURE+ estimator and EM-REG estimators give similar and more conservative estimates. As expected from the simulation, the A-CURE estimator and the regression-based estimators have smaller estimated standard error (SE) than the CURE estimator. Although reductions in SEs may be possible by including interaction and higher-order terms, the limited sample size in this application restricts our ability to explore more complex models for Y. Consequently, we do not recommend the CURE+ and EM-REG estimators in practice unless a large sample size is available. Although the W-REG estimator has smaller SE than the CURE+ and EM-REG estimators, for the same reason we do not recommend this estimator for small samples. Finally, we note that the estimators presented here require us to assume that we have correctly modeled a variety of conditional densities described in Table 4.1 and should be interpreted cautiously. As for all models, the assumptions must be considered in the interpretation, and converging lines of evidence should be sought to clarify causal mechanisms.

4.6 Chapter 4 Discussion

Although a variety of well-established methods are available to estimate causal effects from RCTs, these methods assume that compliance is measured without error. This is an unreasonable assumption in many cases, particularly when compliance is measured by participants' self-report. We explored a variety of weighted estimators, regression-based estimators, and an augmented estimator for use when compliance is measured with error.

All the proposed models performed well when the models were correctly specified. In particular, the regression-based estimators (EM-REG and W-REG) perform well, likely because they are able to average over all participants rather than giving very small weights to some participant. However, the regression-based estimators and the CURE+

estimator do not perform well under misspecification, and they rely on correctly specifying the distribution or mean model for the $Y|A, X, C = 1$ for consistency. For these reasons, we do not recommend them in practice unless investigators have confidence that the model can be at least approximately correctly specified.

Although we did not explore misspecification of the models for the CURE estimator, the CURE estimator has intuitive appeal because it relies primarily on the mixture distribution of the biomarker to discriminate compliers and non-compliers. As we demonstrated via simulation, the A-CURE estimator can be more efficient than the CURE estimator by augmenting with a regression function. The A-CURE estimator has the appealing property of being doubly-robust, but we note that the double robustness only follows by first assuming that the mixture distribution in Equation (4.3) is correctly specified.

The current work has some important limitations. As for all causal methods, the estimators require strong and untestable assumptions, and the causal effects estimated in the application must be interpreted with this in mind. In the application we considered outcomes and compliance during week 6 only. A more thorough analysis may develop a longitudinal extension of these estimators. This is a likely subject of future work.

We developed and evaluated the performance of novel estimators of causal effects when compliance is measured with error. The simulation and application results suggest that the CURE and A-CURE estimators are good choices for investigators, but efficiency gains can be made by using the regression-based estimators if investigators are willing to assume that regression model $Y|A, X, C = 1$ can be specified approximately correctly.

Table 4.1: Chapter 4 Summary of Estimators

Estimator	$f(B\|X,Y,C)$	$E(C\|X)$	$E(C\|X,Y)$	$h(Y\|X,C)$	$E(Y\|X,C)$	Consistent
IPW	–	Y	–	–	–	Yes
REG	–	–	–	–	N	No
A-IPW	–	Y	–	–	N	Yes
CURE	Y	Y	Y	–	–	Yes
CURE+	Y	Y	–	N	N	No
EM-REG	Y	Y	–	N	N	No
W-REG	Y	–	Y	–	N	No
A-CURE	Y	Y	Y	–	N	Yes

Summary of estimators. N: component is not specified correctly; Y: the component is specified correctly. A dash indicates the the component is not estimated. The last column indicates whether the estimator is consistent when $h(Y|X,C)$ or $E(Y|X,C)$ is misspecified.

Table 4.2: Chapter 4 Simulation Results: No Interaction or Quadratic Coefficient, Outliers Removed

	$n = 275$				$n = 550$				$n = 1100$			
Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
IPW	0.013	0.230	0.053	2	0.014	0.158	0.025	4	0.003	0.110	0.012	4
REG	0.006	0.215	0.046	1	0.009	0.145	0.021	4	-0.001	0.102	0.010	3
A-IPW	0.007	0.215	0.046	2	0.010	0.147	0.022	4	-0.001	0.102	0.010	4
CURE	-0.030	0.336	0.114	11	-0.003	0.232	0.054	4	-0.014	0.162	0.026	1
CURE+	0.006	0.287	0.082	6	0.007	0.201	0.041	0	-0.005	0.145	0.021	1
EM-REG	-0.005	0.282	0.079	4	0.000	0.190	0.036	3	-0.006	0.137	0.019	2
W-REG	-0.046	0.346	0.122	8	-0.006	0.229	0.052	3	-0.013	0.156	0.024	2
A-CURE	-0.044	0.343	0.120	10	-0.005	0.229	0.053	3	-0.013	0.156	0.025	2

n_O: number of outliers

Table 4.3: Chapter 4 Simulation Results: Interaction Model Correctly Specified, Outliers Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.028	0.393	0.155	1	0.019	0.273	0.075	2	0.007	0.187	0.035	2
	REG	0.016	0.350	0.123	4	0.013	0.245	0.060	2	0.002	0.171	0.029	1
	A-IPW	0.016	0.350	0.123	4	0.013	0.246	0.061	2	0.002	0.172	0.030	1
	CURE	-0.020	0.478	0.229	18	-0.007	0.326	0.106	4	-0.014	0.225	0.051	1
	CURE+	0.022	0.439	0.193	7	0.013	0.294	0.086	3	-0.001	0.209	0.043	1
	EM-REG	0.006	0.400	0.160	5	0.007	0.273	0.074	1	-0.004	0.195	0.038	1
	W-REG	-0.057	0.454	0.209	5	-0.011	0.299	0.089	4	-0.014	0.211	0.045	0
	A-CURE	-0.050	0.450	0.205	7	-0.010	0.299	0.089	4	-0.014	0.211	0.045	0
2	IPW	0.044	0.607	0.370	1	0.023	0.421	0.177	3	0.012	0.286	0.082	2
	REG	0.020	0.532	0.284	3	0.015	0.371	0.138	3	0.005	0.258	0.066	3
	A-IPW	0.020	0.533	0.284	3	0.015	0.372	0.139	3	0.005	0.258	0.066	3
	CURE	-0.011	0.704	0.496	15	-0.010	0.465	0.216	3	-0.015	0.313	0.098	2
	CURE+	0.036	0.643	0.414	7	0.021	0.426	0.182	5	0.001	0.299	0.089	1
	EM-REG	0.012	0.566	0.321	5	0.011	0.387	0.150	3	-0.001	0.277	0.077	1
	W-REG	-0.049	0.607	0.371	4	-0.007	0.406	0.165	4	-0.012	0.289	0.084	1
	A-CURE	-0.047	0.606	0.370	4	-0.007	0.408	0.166	3	-0.012	0.289	0.084	1

n_O: number of outliers

Table 4.4: Chapter 4 Simulation Results: Quadratic Model Correctly Specified, Outliers Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.019	0.421	0.178	0	0.020	0.288	0.083	1	0.000	0.196	0.039	4
	REG	0.011	0.386	0.149	4	0.016	0.272	0.074	3	-0.001	0.188	0.035	3
	A-IPW	0.012	0.385	0.149	5	0.016	0.273	0.075	2	-0.001	0.188	0.035	3
	CURE	-0.021	0.527	0.278	23	0.001	0.345	0.119	6	-0.015	0.236	0.056	6
	CURE+	0.016	0.471	0.222	3	0.014	0.306	0.094	4	-0.007	0.220	0.048	3
	EM-REG	0.001	0.434	0.188	4	0.010	0.298	0.089	2	-0.007	0.210	0.044	3
	W-REG	-0.059	0.497	0.251	6	-0.013	0.320	0.103	7	-0.020	0.226	0.051	2
	A-CURE	-0.062	0.496	0.250	9	-0.013	0.322	0.104	6	-0.020	0.226	0.051	2
2	IPW	0.029	0.685	0.470	1	0.024	0.465	0.217	2	0.002	0.313	0.098	6
	REG	0.017	0.632	0.399	2	0.021	0.449	0.202	0	-0.001	0.303	0.092	4
	A-IPW	0.017	0.632	0.400	2	0.021	0.449	0.202	0	-0.002	0.302	0.091	5
	CURE	-0.017	0.814	0.663	25	0.004	0.519	0.269	6	-0.017	0.350	0.123	7
	CURE+	0.025	0.739	0.547	1	0.020	0.475	0.226	2	-0.009	0.330	0.109	6
	EM-REG	0.010	0.671	0.450	1	0.013	0.463	0.215	0	-0.006	0.316	0.100	6
	W-REG	-0.057	0.714	0.513	3	-0.008	0.474	0.225	3	-0.021	0.330	0.109	4
	A-CURE	-0.060	0.717	0.518	4	-0.007	0.475	0.225	3	-0.021	0.330	0.109	4

n_O: number of outliers

Table 4.5: Chapter 4 Simulation Results: Misspecified Interaction Model, Outliers Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.028	0.393	0.155	1	0.019	0.273	0.075	2	0.007	0.187	0.035	2
	REG	-0.031	0.377	0.143	3	-0.033	0.265	0.071	1	-0.042	0.182	0.035	3
	A-IPW	0.004	0.384	0.147	5	0.005	0.269	0.072	2	-0.002	0.185	0.034	3
	CURE	-0.020	0.478	0.229	18	-0.007	0.326	0.106	4	-0.014	0.225	0.051	1
	CURE+	0.165	0.536	0.315	16	0.205	0.335	0.154	10	0.196	0.236	0.094	4
	EM-REG	-0.004	0.507	0.257	20	0.047	0.321	0.105	7	0.038	0.229	0.054	1
	W-REG	-0.091	0.510	0.268	6	-0.052	0.336	0.116	3	-0.056	0.233	0.057	0
	A-CURE	-0.044	0.524	0.277	11	-0.006	0.340	0.116	5	-0.011	0.232	0.054	1
2	IPW	0.044	0.607	0.370	1	0.023	0.421	0.177	3	0.012	0.286	0.082	2
	REG	-0.068	0.608	0.374	1	-0.076	0.425	0.187	1	-0.083	0.291	0.091	3
	A-IPW	0.002	0.616	0.380	6	0.001	0.436	0.190	2	-0.003	0.298	0.089	4
	CURE	-0.011	0.704	0.496	15	-0.010	0.465	0.216	3	-0.015	0.313	0.098	2
	CURE+	-0.501	1.862	3.719	163	-0.291	1.342	1.886	139	0.298	0.463	0.303	219
	EM-REG	-0.679	2.727	7.898	92	-0.782	1.579	3.106	138	0.118	0.342	0.131	268
	W-REG	-0.133	0.750	0.580	9	-0.095	0.499	0.258	3	-0.097	0.348	0.131	0
	A-CURE	-0.048	0.773	0.601	17	-0.005	0.512	0.262	6	-0.008	0.351	0.123	1

n_O: number of outliers

Table 4.6: Chapter 4 Simulation Results: Misspecified Quadratic Model, Outliers Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.019	0.421	0.178	0	0.020	0.288	0.083	1	0.000	0.196	0.039	4
	REG	-0.121	0.448	0.216	1	-0.109	0.320	0.115	1	-0.121	0.216	0.061	3
	A-IPW	-0.018	0.456	0.209	6	0.002	0.338	0.114	1	-0.014	0.222	0.050	4
	CURE	-0.021	0.527	0.278	23	0.001	0.345	0.119	6	-0.015	0.236	0.056	6
	CURE+	0.406	0.528	0.444	38	0.421	0.344	0.296	28	0.407	0.247	0.226	5
	EM-REG	0.204	0.499	0.291	46	0.222	0.338	0.163	29	0.205	0.237	0.098	7
	W-REG	-0.204	0.614	0.419	5	-0.133	0.390	0.170	6	-0.136	0.272	0.092	1
	A-CURE	-0.060	0.625	0.394	21	-0.006	0.414	0.171	4	-0.019	0.277	0.077	2
2	IPW	0.029	0.685	0.470	1	0.024	0.465	0.217	2	0.002	0.313	0.098	6
	REG	-0.253	0.776	0.667	1	-0.230	0.553	0.358	2	-0.240	0.373	0.197	2
	A-IPW	-0.043	0.800	0.641	5	-0.009	0.589	0.347	3	-0.025	0.386	0.150	5
	CURE	-0.017	0.814	0.663	25	0.004	0.519	0.269	6	-0.017	0.350	0.123	7
	CURE+	-0.642	7.491	56.521	65	-0.949	8.417	71.739	43	-2.598	7.127	57.543	30
	EM-REG	5.412	6.067	66.095	8	6.071	5.928	71.991	3	6.000	5.379	64.937	0
	W-REG	-0.354	0.991	1.108	8	-0.259	0.644	0.481	4	-0.258	0.440	0.260	2
	A-CURE	-0.099	1.032	1.076	24	-0.011	0.687	0.473	6	-0.023	0.457	0.209	4

n_O: number of outliers

Table 4.7: Chapter 4 Simulation Results: No Interaction or Quadratic Coefficient, Outliers Not Removed

	$n = 275$				$n = 550$				$n = 1100$			
Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
IPW	0.011	0.232	0.054	2	0.013	0.161	0.026	4	0.001	0.112	0.013	4
REG	0.005	0.217	0.047	1	0.009	0.147	0.022	4	-0.001	0.104	0.011	3
A-IPW	0.006	0.218	0.047	2	0.009	0.149	0.022	4	-0.001	0.104	0.011	4
CURE	-0.031	0.373	0.140	11	-0.006	0.237	0.056	4	-0.015	0.163	0.027	1
CURE+	0.009	0.324	0.105	6	0.007	0.201	0.041	0	-0.005	0.146	0.021	1
EM-REG	-0.001	0.302	0.091	4	0.002	0.193	0.037	3	-0.006	0.138	0.019	2
W-REG	-0.045	0.368	0.137	8	-0.008	0.232	0.054	3	-0.014	0.157	0.025	2
A-CURE	-0.046	0.364	0.135	10	-0.007	0.233	0.054	3	-0.014	0.158	0.025	2

n_O: number of outliers

Table 4.8: Chapter 4 Simulation Results: Interaction Model Correctly Specified, Outliers Not Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.027	0.395	0.157	1	0.019	0.277	0.077	2	0.006	0.189	0.036	2
	REG	0.014	0.356	0.127	4	0.013	0.247	0.061	2	0.002	0.172	0.030	1
	A-IPW	0.014	0.357	0.128	4	0.013	0.248	0.062	2	0.002	0.173	0.030	1
	CURE	-0.032	0.573	0.330	18	-0.009	0.333	0.111	4	-0.015	0.227	0.052	1
	CURE+	0.020	0.452	0.205	7	0.012	0.298	0.089	3	-0.002	0.210	0.044	1
	EM-REG	0.005	0.409	0.167	5	0.006	0.274	0.075	1	-0.003	0.196	0.039	1
	W-REG	-0.062	0.467	0.222	5	-0.013	0.305	0.093	4	-0.014	0.211	0.045	0
	A-CURE	-0.058	0.468	0.222	7	-0.013	0.305	0.093	4	-0.014	0.211	0.045	0
2	IPW	0.042	0.610	0.374	1	0.024	0.428	0.184	3	0.012	0.289	0.084	2
	REG	0.022	0.540	0.292	3	0.016	0.377	0.142	3	0.006	0.261	0.068	3
	A-IPW	0.022	0.541	0.293	3	0.017	0.378	0.143	3	0.006	0.261	0.068	3
	CURE	-0.023	0.835	0.698	15	-0.011	0.473	0.224	3	-0.015	0.317	0.101	2
	CURE+	0.034	0.663	0.441	7	0.017	0.437	0.191	5	0.002	0.300	0.090	1
	EM-REG	0.014	0.580	0.336	5	0.010	0.393	0.155	3	0.000	0.279	0.078	1
	W-REG	-0.053	0.619	0.386	4	-0.010	0.415	0.172	4	-0.011	0.290	0.084	1
	A-CURE	-0.051	0.618	0.385	4	-0.009	0.414	0.172	3	-0.011	0.290	0.084	1

n_O: number of outliers

Table 4.9: Chapter 4 Simulation Results: Quadratic Model Correctly Specified, Outliers Not Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.019	0.421	0.178	0	0.018	0.289	0.084	1	0.002	0.200	0.040	4
	REG	0.013	0.393	0.155	4	0.016	0.276	0.076	3	-0.000	0.191	0.036	3
	A-IPW	0.013	0.394	0.155	5	0.015	0.276	0.076	2	-0.000	0.191	0.036	3
	CURE	-0.055	0.694	0.484	23	-0.004	0.358	0.128	6	-0.017	0.247	0.061	6
	CURE+	0.014	0.479	0.229	3	0.012	0.312	0.097	4	-0.006	0.224	0.050	3
	EM-REG	0.004	0.443	0.196	4	0.008	0.301	0.090	2	-0.005	0.214	0.046	3
	W-REG	-0.071	0.557	0.316	6	-0.018	0.330	0.109	7	-0.018	0.228	0.052	2
	A-CURE	-0.002	2.385	5.688	9	-0.017	0.331	0.110	6	-0.018	0.228	0.052	2
2	IPW	0.027	0.688	0.474	1	0.024	0.469	0.221	2	0.002	0.321	0.103	6
	REG	0.021	0.637	0.407	2	0.021	0.449	0.202	0	0.001	0.309	0.095	4
	A-IPW	0.021	0.638	0.408	2	0.021	0.449	0.202	0	0.001	0.309	0.095	5
	CURE	-0.063	1.090	1.192	25	0.000	0.539	0.290	6	-0.019	0.367	0.135	7
	CURE+	0.022	0.744	0.554	1	0.017	0.480	0.231	2	-0.007	0.339	0.115	6
	EM-REG	0.012	0.675	0.455	1	0.013	0.463	0.215	0	-0.004	0.325	0.106	6
	W-REG	-0.061	0.729	0.536	3	-0.013	0.481	0.232	3	-0.017	0.336	0.113	4
	A-CURE	-0.046	0.908	0.827	4	-0.012	0.481	0.232	3	-0.017	0.336	0.113	4

n_O: number of outliers

Table 4.10: Chapter 4 Simulation Results: Misspecified Interaction Model, Outliers Not Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
	IPW	0.027	0.395	0.157	1	0.019	0.277	0.077	2	0.006	0.189	0.036	2
	REG	-0.030	0.383	0.148	3	-0.034	0.266	0.072	1	-0.041	0.185	0.036	3
	A-IPW	0.008	0.394	0.155	5	0.005	0.272	0.074	2	-0.001	0.188	0.036	3
	CURE	-0.032	0.573	0.330	18	-0.009	0.333	0.111	4	-0.015	0.227	0.052	1
	CURE+	0.136	0.605	0.385	16	0.195	0.360	0.167	10	0.194	0.241	0.096	4
	EM-REG	-0.046	0.699	0.490	20	0.040	0.339	0.117	7	0.039	0.230	0.055	1
	W-REG	-0.102	0.528	0.289	6	-0.056	0.340	0.119	3	-0.056	0.233	0.057	0
	A-CURE	-0.039	0.570	0.326	11	-0.007	0.348	0.121	5	-0.011	0.233	0.054	1
2	IPW	0.042	0.610	0.374	1	0.024	0.428	0.184	3	0.012	0.289	0.084	2
	REG	-0.066	0.612	0.379	1	-0.077	0.427	0.189	1	-0.082	0.295	0.094	3
	A-IPW	0.010	0.636	0.405	6	0.001	0.440	0.194	2	-0.001	0.304	0.093	4
	CURE	-0.023	0.835	0.698	15	-0.011	0.473	0.224	3	-0.015	0.317	0.101	2
	CURE+	-0.647	4.485	20.535	163	-0.524	4.592	21.358	139	0.169	5.693	32.437	219
	EM-REG	-0.137	4.050	16.421	92	0.112	3.228	10.435	138	0.263	2.625	6.957	268
	W-REG	-0.153	0.792	0.650	9	-0.100	0.506	0.266	3	-0.097	0.348	0.131	0
	A-CURE	-0.042	0.871	0.760	17	-0.005	0.528	0.278	6	-0.007	0.353	0.124	1

n_O: number of outliers

Table 4.11: Chapter 4 Simulation Results: Misspecified Quadratic Model, Outliers Not Removed

		$n = 275$				$n = 550$				$n = 1100$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.019	0.421	0.178	0	0.018	0.289	0.084	1	0.002	0.200	0.040	4
	REG	-0.123	0.451	0.218	1	-0.110	0.322	0.116	1	-0.121	0.218	0.062	3
	A-IPW	-0.011	0.472	0.223	6	0.003	0.340	0.116	1	-0.011	0.227	0.052	4
	CURE	-0.055	0.694	0.484	23	-0.004	0.358	0.128	6	-0.017	0.247	0.061	6
	CURE+	0.433	1.349	2.007	38	0.462	1.592	2.748	28	0.459	1.174	1.588	5
	EM-REG	0.471	1.447	2.315	46	0.389	1.084	1.326	29	0.224	0.407	0.216	7
	W-REG	-0.214	0.632	0.445	5	-0.139	0.402	0.181	6	-0.137	0.273	0.093	1
	A-CURE	0.806	19.026	362.623	21	-0.006	0.422	0.178	4	-0.016	0.284	0.081	2
2	IPW	0.027	0.688	0.474	1	0.024	0.469	0.221	2	0.002	0.321	0.103	6
	REG	-0.251	0.780	0.671	1	-0.230	0.557	0.363	2	-0.240	0.376	0.199	2
	A-IPW	-0.028	0.827	0.685	5	-0.003	0.601	0.361	3	-0.021	0.396	0.158	5
	CURE	-0.063	1.090	1.192	25	0.000	0.539	0.290	6	-0.019	0.367	0.135	7
	CURE+	0.125	9.009	81.179	65	-0.155	9.475	89.806	43	-1.995	8.327	73.316	30
	EM-REG	5.618	6.470	73.420	8	6.171	6.215	76.707	3	6.000	5.379	64.937	0
	W-REG	-0.381	1.034	1.215	8	-0.263	0.657	0.501	4	-0.258	0.444	0.263	2
	A-CURE	0.849	20.764	431.877	24	-0.000	0.715	0.512	6	-0.017	0.478	0.228	4

n_O: number of outliers

Table 4.12: Chapter 4 Application Results

Estimator	$\hat{\mu}(2,0)$	$\hat{\mu}(1,0)$	$\hat{\mu}(2,0) - \hat{\mu}(1,0)$	SE	95% CI
ITT	22.18	15.37	6.81	1.57	(3.78, 10.07)
Causal Estimators					
CURE	22.18	14.98	7.20	2.87	(1.46, 11.63)
CURE+	22.18	16.98	5.20	3.11	(0.36, 11.97)
EM-REG	22.18	16.80	5.38	2.73	(1.56, 12.54)
W-REG	22.18	15.53	6.65	2.48	(1.85, 11.58)
A-CURE	22.18	15.47	6.71	2.55	(1.75, 11.48)

Point estimates, standard error of the estimators, and 95% confidence interval of the estimated causal effect for each estimator. $\mu(2,0)$: mean cigarettes smoked per day for the usual brand group. $\mu(1,0)$: mean cigarettes smoked per day for the VLNC group if all participants were to be compliant.

Chapter 5

Conclusion

Causal inference is often one of the primary goals of public health research, but establishing and estimating causal effects can be complicated due to confounding in observational data or in RCTs with noncompliance. We considered two non-standard situations and proposed novel causal estimators for these scenarios.

In Chapter 2, we developed estimators for the causal effect of solid organ transplantation treatment regimes. Standard IPCW estimators have an important limitation in this context: they estimate the anticipated survival for a random patient who adopts a treatment regime. This may have relevance for individual patients, but it may have limited usefulness for public health researchers. A more meaningful analysis would estimate the anticipated survival for a random patient assuming that the entire population of patients on the transplantation waiting list adopt the strategy. We developed a class of estimators that can estimate causal effects for either scenario, so that the analysis can be tailored to appropriately address the question of interest. We developed the estimators to estimate the anticipated survival for pre-specified treatment regimes but did not attempt to identify an optimal treatment regime that maximizes the anticipated survival probability. The method could potentially be modified to identify an optimal treatment regime using, for example, functional regression, where the survival curve is the outcome, and parameters defining the regime are predictors.

In Chapters 3 and 4, we considered estimators of causal effects from RCTs with imperfect measures of compliance. The proposed estimators were strongly motivated by a

regulatory tobacco RCT, but we argued that compliance is frequently measured with error in other settings as well. Rather than relying on an imperfect measure of compliance, we treated compliance as an unobserved variable and showed how to construct weights by using the available data to estimate the conditional probability of compliance, leading to consistent estimators of causal effects. An interesting question is whether the estimators proposed in this dissertation can be advantageous even if the compliance is measured without error. As we briefly discussed in Chaper 3, when all conditional expectations are known, the CURE estimator is more efficient asymptotically than traditional IPCW. In most cases, however, the expectations must be estimated from the data, and any possible efficiency gains due to the CURE estimator come at the cost of needing additional modeling assumptions. A thorough investigation of the costs and benefits of the proposed estimators when compliance is measured without error could be useful here. In addition, we considered a point exposure study with a single outcome for simplicity, but development of longitudinal extensions of the CURE estimator is a natural direction for future work. Although it seems clear that a longitudinal extension could be developed in the case where biomarkers and outcomes are available simultaneously, it is less clear how to deal with the more realistic situation where biomarkers are only available at limited time points. For example, in the CENIC-p1 trial, biomarkers of nicotine exposure were collected at baseline and at weeks 2 and 6, whereas cigarette consumption was collected daily for the entire 6-week study. It is not immediately clear how a longitudinal extension could be implemented that makes use of all outcome data when only limited biomarker data are available. Restricting analyses to time points with complete biomarker-outcome pairs is not ideal, because this would discard outcome data from other time points, but modifying the estimators in Chapters 3 and 4 to accommodate limited biomarker data is not trivial. This is an area that merits further investigation.

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Appendix A

Chapter 2 Appendix

A.1 Notation

$T^*(\infty)$: potential survival time from listing if a patient were to never receive a transplanted organ

$T^*(b, q)$: potential survival time from listing if a patient received an organ b days after listing with organ characteristics q

$\mathcal{Q}$: the set of all donor characteristics

$X^*(b)$ the covariates collected b days after listing for a random patient including whether or not the patient had been previously transplanted and had previously died prior to time b

L_i: calendar date the ith patient is listed for organ transplantation

$N_{ij}^*(t, q)$: indicator that patient died on the jth study day if she accepted an organ with characteristics q, t days after listing

$Y_{ij}^*(t, q)$: indicator that patient was at risk of death on the jth study day if she accepted an organ with characteristics q, t days after listing

$N_{ij}^*(\infty)$: indicator that patient died on the jth study day if she were to never receive a transplant

$Y_{ij}^*(\infty)$: indicator that patient was at risk of death on the jth study day if she were to never receive a transplant

g: a transplant regime dictating which organs should be avoided

$\mathcal{G}$: the set of all possible treatment regimes

$T_i^*(g, g')$: the time from listing a patient would live if she where to follow regime g and all other patients were to follow g'

$B^{(g,g')}$: time from listing until transplantation for a patient who follows regime g while all other patients follow regime g'

$Q^{(g,g')}$: vector of the transplanted organ characteristics for a patient who follows regime g while all other patients follow regime g'

$\mathcal{P}_i$: the set of potential outcomes for the ith patient

$f_{T^*(g,g')}(t)$: the density of $T^*(g, g')$

$f_{T^*(B,Q)|\overline{X}^*(b)}\{t|\overline{x}(b)\}$: the conditional density of $T^*(b, q)$

$\rho^{(g,g')}\{b, q|\overline{x}(b)\}$: the probability of receiving a transplant b days after listing with organ characteristics q given she is untransplanted $b-1$ days after listing with covariate history $\overline{x}(b)$ and the patient follows regime g while all others follow regime g'

$f_{T,Q|\overline{X}^*(t)}^{(g,g')}\{t, q|\overline{x}(t)\}$: the probability of receiving a transplant t days after listing with organ characteristics q if the patient follows regime g while all others follow regime g'

$f_{\overline{X}(b)}$: the density of $\overline{X}(b)$

T_i: the observed time from entering the waiting list until death

X_{ij}: the vector of covariates collected on the ith patient on the jth day

N_{ij}: indicator for whether patient died on the jth study day

Y_{ij}: indicator for whether patient was at risk for death on the jth study day

S_j: number of organs available on the jth study day

Q_{jk}: characteristics of the kth organ on the jth day

A_{ijk}: indicator for whether the patient was transplanted with the kth organ on the jth day

O_{ijk}: indicator for whether the patient was offered the kth organ on the jth day

E_{ijk}: the collection of all information on the ith subject at the time of the kth transplant on the jth day but excluding whether the ith patient actually receives the kth organ

$E_{\cdot jk}$: the collection of information on all subjects $i = 1, \ldots, n$ prior to assigning the kth organ on the jth study day

R_{ijk}: the rank of the ith patient on the waiting list for the kth organ on the jth day of the study

$D_{ijk}(g, E_{ijk})$: indicator for whether or not the kth organ on day j should be avoided under regime g based on the organ and patient characteristics

$\pi_{ijk}^{A(g)}(E_{ijk})$: the probability that the ith patient accepts the kth organ on the jth day if the patient is complying with or following regime g.

$\emptyset$: the transplant regime where patients make no changes to their propensity to accept or decline organs

$\pi_{ijk}^{A(\emptyset)}(E_{ijk})$: the probability that the ith patient accepts the kth organ on the jth day if the patient makes no changes to her organ acceptance policy.

$\pi_{ijk}^{O(g,g')}(E_{\cdot jk})$: the conditional probability the ith patient is offered the kth organ on day j given that she is following regime g and all other patients are following regime g'

$\pi_{ijk}^{(g,g')}(a_{ijk}, E_{\cdot jk})$: the probability that ith person receives and does not receive if $a_{ijk} = 1$ and $a_{ijk} = 0$, respectively, the kth available organ on the jth day given all information up until the time of assigning that organ, assuming the ith patient is following regime g and all other patients are following regime g'.

$\overline{\pi}_{ij}^{(g,g')}(\overline{a}_{ij}, \overline{E}_{jS_j})$: the probability that the ith patient has her treatment history through study day j given that she is following regime g and all other patients follow regime g'

$S_r(g, g')$: the survival probability r days after entering the waiting list for following regime g while all other patients follow regime g'

$\lambda_t(g, g')$: the discrete-time hazard of death t days after entering the waiting list for a randomly selected patient if she were to following regime g and all other patients followed regime g'

λ_t^{PT}: the post-transplantation discrete-time hazard of death t days after transplantation

A.2 Additional Application Tables

Table A.1: Lung Quality Model Coefficient Estimates and 95% Confidence Intervals

Coefficient	Estimate	95% C.I.
Patient Age	-0.029	(-0.041, -0.017)
Patient Age′	0.041	(0.026, 0.056)
Patient Age″	-0.320	(-0.566, -0.073)
Donor Age	0.000	(-0.017, 0.017)
Donor Age′	-0.045	(-0.143, 0.052)
Donor Age″	0.098	(-0.069, 0.265)
LAS	0.049	(0.015, 0.084)
LAS′	-0.985	(-1.846, -0.124)
LAS″	1.565	(0.175, 2.954)
I(Donor Diabetes = Y)	0.257	(0.103, 0.411)
I(Disease Group = B)	0.204	(-0.020, 0.427)
I(Disease Group = C)	-0.219	(-0.433, -0.006)
I(Disease Group = D)	-0.126	(-0.253, 0.000)
I(Single-Lung Transplant)	0.115	(0.023, 0.207)
I(Patient on Life Support)	0.441	(0.278, 0.604)
I(Donor Race = other)	-0.199	(-0.323, -0.074)
I(Donor Race = white)	-0.269	(-0.368, -0.170)
Patient-Donor Height Difference	-0.003	(-0.017, 0.011)
Patient-Donor Height Difference′	-0.024	(-0.073, 0.026)
Patient-Donor Height Difference″	0.104	(-0.071, 0.280)
Patient BMI	0.012	(0.002, 0.022)

Coefficient estimates from the Cox proportional hazards model used to estimate donor quality. Coefficients for the restricted cubic spline bases are indicated by ′ and ″.

Table A.2: Logistic Regression Model Coefficients and 95% Confidence Intervals For Accepting a Transplantation.

Coefficient	Estimate	95%C.I.
Intercept	0.649	(-0.190, 1.488)
Current Age	-0.025	(-0.034, -0.017)
Current Age′	0.055	(0.043, 0.067)
Current Age″	-0.469	(-0.583, -0.355)
LAS	0.029	(0.006, 0.052)
LAS′	-0.046	(-0.426, 0.334)
LAS″	0.062	(-0.587, 0.711)
Days on Waiting List	-0.008	(-0.009, -0.007)
Days on Waiting List′	0.149	(0.118, 0.179)
Days on Waiting List″	-0.211	(-0.255, -0.167)
Disease Group = B	-0.967	(-1.099, -0.834)
Disease Group = C	-0.289	(-0.414, -0.164)
Disease Group = D	-0.614	(-0.686, -0.542)
Height Difference	0.103	(0.096, 0.111)
Height Difference′	-0.317	(-0.338, -0.295)
Height Difference″	0.863	(0.749, 0.976)
I(Donor Smoker $\geq$ 20 pack-years)	-0.227	(-0.302, -0.151)
I(Donor Age $>$ 50)	-1.669	(-2.378, -0.961)
Current Age $\cdot$ I(Donor Age $>$ 50)	0.028	(0.007, 0.048)
Current Age' $\cdot$ I(Donor Age $>$ 50)	-0.002	(-0.034, 0.029)
Current Age" $\cdot$ I(Donor Age $>$ 50)	0.015	(-0.266, 0.295)

Coefficient estimates from the logistic model used to estimate the probability of accepting an offered organ. Coefficients for the restricted cubic spline bases are indicated by ′ and ″.

Appendix B

Chapter 3 Appendix

B.1 EM Algorithm M Step Updates for α and ξ

Here we give details on the EM algorithm updates for α and ξ, the coefficient vector for $\rho(a, x, y, d; \alpha) = \Pr(C = 1|A = a, X = x, Y = y, D = d; \alpha)$ and $f(B|A, X, Y, D, C; \xi)$, the conditional density of B given A, X, Y, D, C, discussed in Section 3.3.1. We use notation from Boos and Stefanski (2013). Random vectors are denoted with bold type, e.g. $\boldsymbol{A} = (A_1, \ldots, A_n)^T$.

The complete data log likelihood for $\boldsymbol{\theta} = (\xi^T, \alpha^T)^T$ is

$$\begin{aligned} L(\boldsymbol{\theta}|\boldsymbol{A}, \boldsymbol{B}, \boldsymbol{X}, \boldsymbol{Y}, \boldsymbol{D}, \boldsymbol{C}) = &\sum_{i=1}^{n} \{C_i \log f(B_i|A_i, X_i, Y_i, D_i, c = 1) + \\ &\qquad (1 - C_i) \log f(B_i|A_i, X_i, Y_i, D_i, c = 0)\} + \\ &C_i \log \rho(A_i, X_i, Y_i, D_i; \alpha) + \\ &(1 - C_i) \log \{1 - \rho(A_i, X_i, Y_i, D_i; \alpha)\}. \end{aligned}$$

The conditional expectation of the E step is given by

$$\begin{aligned} Q(\boldsymbol{\theta}, \boldsymbol{\theta}^{(\nu)}, \boldsymbol{A}, \boldsymbol{B}, \boldsymbol{X}, \boldsymbol{Y}, \boldsymbol{D}, \boldsymbol{C}) = &E_{\boldsymbol{\theta}^{(\nu)}} \{\log L(\boldsymbol{\theta}|\boldsymbol{A}, \boldsymbol{B}, \boldsymbol{X}, \boldsymbol{Y}, \boldsymbol{D}, \boldsymbol{C})|\boldsymbol{A}, \boldsymbol{B}, \boldsymbol{X}, \boldsymbol{Y}, \boldsymbol{D}\} \\ = &\sum_{i=1}^{n} \Big\{ w_i^{(\nu)} \log f(B_i|A_i, X_i, Y_i, D_i, c = 1) + \\ &\qquad (1 - w_i^{(\nu)}) \log f(B_i|A_i, X_i, Y_i, D_i, c = 0) \Big\} + \\ &w_i^{(\nu)} \log \rho(A_i, X_i, Y_i, D_i; \alpha) + \\ &(1 - w_i^{(\nu)}) \log \{1 - \rho(A_i, X_i, Y_i, D_i; \alpha)\} \end{aligned}$$

where

$$
\begin{aligned}
w_i^{(\nu)} &= E_{\boldsymbol{\theta}^{(\nu)}}(C_i|A_i, B_i, X_i, Y_i, D_i) \\
&= \frac{f(B_i|A_i, X_i, Y_i, D_i, c=1; \xi^{(\nu)}) \cdot \rho(A_i, X_i, Y_i, D_i; \alpha^{(\nu)})}{f(B_i|A_i, X_i, Y_i, D_i, c=1; \xi^{(\nu)}) \cdot c \cdot \rho(A_i, X_i, Y_i; \alpha^{(\nu)}) + (1-c) \cdot \left\{1 - \rho(A_i, X_i, Y_i; \alpha^{(\nu)})\right\}}.
\end{aligned}
$$

The M step update $\alpha^{(\nu+1)}$ is the solution to the score equations

$$
\sum_{i=1}^{n} \frac{w_i^{(\nu)} - \rho(A_i, B_i, X_i, Y_i, D_i; \alpha)}{\rho(A_i, B_i, X_i, Y_i, D_i; \alpha)\left\{1 - \rho(A_i, B_i, X_i, Y_i, D_i; \alpha)\right\}} \frac{\partial \rho(A_i, B_i, X_i, Y_i, D_i; \alpha)}{\partial \alpha^T} = 0.
$$

If there are no shared parameters in the conditional density of the biomarker among the compliers and noncompliers, then the M step update $\xi^{(\nu+1)}$ is the solution to the weighted score equations

$$
\sum_{i=1}^{n} \frac{\partial \log f(B_i|A_i, X_i, Y_i, D_i, c=1; \xi_C)}{\partial \xi_C^T} w_i^{(\nu)} = 0
$$

$$
\sum_{i=1}^{n} \frac{\partial \log f(B_i|A_i, X_i, Y_i, D_i, c=0; \xi_{NC})}{\partial \xi_{NC}^T} (1 - w_i^{(\nu)}) = 0,
$$

where ξ_C and ξ_{NC} are the parameters corresponding to the distribution of the compliers and non-compliers.

B.2 Directed Acyclic Graph assumed in Simulation and Application

Figure B.1 shows one possible Directed Acyclic Graph (DAG) for the CENIC-p1 data and other possible applications. The arrows between B and Y are dashed because CENIC-p1 is a unique trial in that the DAG has the causal relationship $Y \to B$, i.e., the outcome, the number of cigarettes smoked, causes the biomarker, TNE. The arrow from X to B is dotted because, in our simulation and application, we assume that this arrow does not exist; if this arrow is removed, the DAG implies that X and B are conditionally independent given A, Y and C. This simplifies the estimation of the conditional density of B given A, B, X, and Y, but we note that this is assumption is not required for the method in general.

In contrast, the DAG in many clinical trials would have $B \to Y$. For example, in a clinical trial investigating blood pressure-lowering medication, we might expect that B, the circulating levels of medication or a metabolite, would cause the amount of decrease in blood pressure Y. In this case, it may be more intuitive to model the conditional density of Y given A, B, X, D, C and $\Pr(C = 1|A, B, X, D)$ in estimating the numerator of the weights.

We also note that in some scenarios, it may be reasonable to assume that confounders X or the response Y cause the subject to report compliance honestly, H. The proposed method still provides consistent estimation of the causal effect.

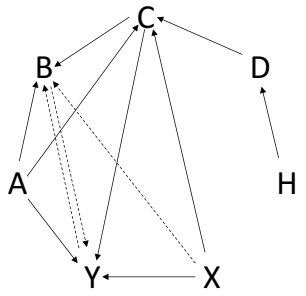

Figure B.1: A Possible Directed Acyclic Graph (DAG) for the CENIC-p1 Data

B.3 Additional Application Tables

Table B.1: Estimated mixture distribution coefficients and parameters

Component	$\hat{\gamma_0}$	$\hat{\gamma_1}$	$\hat{\sigma}$
Compliant ($C = 1$)	0.12(-0.96, 1.19)	0.02(-0.01, 0.07)	0.89(0.55, 1.34)
Non-compliant ($C = 0$)	3.33(2.79, 4.13)	0.01(-0.04, 0.04)	0.78(0.51, 1.13)

Estimated mixture distribution coefficients and parameters (95% bootstrap percentile intervals) assuming $B|Y, C, D = 1 \sim N(\gamma_0 + \gamma_1 Y, \sigma^2)$. $B = \log(TNE)$, $Y =$ study cigarettes smoked per day.

Table B.2: Estimated coefficients for the mixture distribution logistic model $\Pr(C = 1|A = 1, X, Y, D = 1)$

Coefficient	Estimate	95% CI
Intercept	1.261	(-2.396, 14.724)
Age	0.017	(-0.031, 0.083)
Baseline log(TNE)	-0.944	(-3.642, -0.440)
Baseline Cigarettes per day	-0.011	(-0.188, 0.222)
Max Symptoms Week 1	0.027	(-0.088, 0.153)
MNWS Week 5	0.086	(-0.081, 0.292)
QSU Study Cigarettes Week 5	0.045	(-0.021, 0.314)
QSU Usual Brand Cigarettes Week 5	-0.048	(-0.219, -0.005)
CES Satisfaction Week 5	0.202	(-0.469, 0.846)
Y (Study Cigarettes per day)	-0.004	(-0.251, 0.116)

Estimated coefficients and 95% bootstrap percentile confidence intervals for the mixture distribution logistic model $\Pr(C = 1|A = 1, X, Y, D = 1)$. MNWS: Minnesota Nicotine Withdrawal Scale, higher scores indicating greater withdrawal symptoms. QSU: Questionnaire of Smoking Urges, higher scores indicating greater urges. CES: Cigarette Evaluation Scale, higher scores indicating greater satisfaction with study cigarettes.

Table B.3: Estimated coefficients for logistic model for denominator of weights

Coefficient	Estimate	95% CI
Intercept	-0.707	(-4.092, 5.104)
Age	0.022	(-0.029, 0.082)
Baseline log(TNE)	-0.475	(-1.698, 0.042)
Baseline Cigarettes per day	-0.059	(-0.205, 0.022)
Max Symptoms Week 1	0.013	(-0.087, 0.123)
MNWS Week 5	0.050	(-0.109, 0.230)
QSU Study Cigarettes Week 5	0.013	(-0.063, 0.127)
QSU Usual Brand Cigarettes Week 5	-0.030	(-0.144, 0.009)
CES Satisfaction Week 5	0.418	(-0.216, 1.043)

Estimated coefficients and 95% bootstrap confidence intervals for logistic model for denominator of weights. MNWS: Minnesota Nicotine Withdrawal Scale, higher scores indicating greater withdrawal symptoms. QSU: Questionnaire of Smoking Urges, higher scores indicating greater urges. CES: Cigarette Evaluation Scale, higher scores indicating greater satisfaction with study cigarettes.

Table B.4: Participant Characteristics

	Self-Report		Estimated $\Pr(C = 1 \mid B, X, Y, D)$	
Characteristic	Non-Compliant	Compliant	<=0.5	> 0.5
n	88	137	169	49
Male	45(51%)	74(54%)	92(54%)	22(45%)
Female	43(49%)	63(46%)	77(46%)	27(55%)
White	46(52%)	75(55%)	87(51%)	28(57%)
Black	32(36%)	47(34%)	62(37%)	17(35%)
Other	10(11%)	15(11%)	20(12%)	4(8%)
Age	40.14(13.14)	42.48(13.37)	40.57(13.04)	44.90(13.83)
Baseline log(TNE)	3.71(0.94)	3.69(0.84)	3.79(0.84)	3.44(0.88)
Baseline Cigarettes per day	16.78(8.41)	14.78(6.83)	15.96(7.46)	13.83(6.40)
Max Symptoms Week 1	12.85(7.30)	12.00(7.03)	12.10(7.22)	12.31(6.73)
MNWS Week 5	7.27(5.27)	6.13(4.82)	6.38(4.86)	6.88(5.36)
QSU Study				
Cigarettes Week 5	19.69(13.80)	20.32(12.90)	19.46(12.96)	22.43(14.43)
QSU Usual Brand				
Cigarettes Week 5	29.42(16.60)	25.70(16.33)	27.62(16.70)	24.78(15.21)
CES Satisfaction Week 5	2.06(1.13)	2.79(1.46)	2.33(1.33)	3.15(1.43)
Week 6 log(TNE)*	3.43(2.93, 4.10)	2.28(0.86, 3.80)	3.47(2.93, 4.07)	0.29(-0.40, 0.99)

Baseline characteristics, confounders, and the biomarker week 6 log(TNE) for the application. Values given are n(%) for categorical variables and mean(sd) for numeric variables. *Mean(1^{st} quartile, 3^{rd} quartile)

B.4 Measurement Error in Y

Throughout the Chapter 3 we assumed that correctly or incorrectly reporting compliance has no effect on the self-reported outcome, that is, i.e. D does not affect Y. We note that many clinical trials rely on self-reported compliance but use endpoints which are direct physiologic measures or adjudicated clinical events. For example, in CENIC-p1, ITT estimates of the effect of nicotine level on other physiologic endpoints including expired carbon monoxide were included in the primary analysis (Donny *and others*, 2015).

Furthermore, under very plausible assumptions concerning the self-reported error of cigarette consumption, we can still obtain consistent estimators of the causal effect. In particular, assume that Y is the outcome without any self-report or measurement error and we are interested in estimating $E\{Y^*(a,0)\}$, the average effect if possibly contrary to fact all subjects were assigned treatment group a, fully complied with the assigned treatment, and there was no measurement error in the response. Instead of observing Y directly, we observe $W = Y + \epsilon$, where ϵ is the self-report or measurement error. In this case, the CURE estimator becomes

$$\sum_{i=1}^{n} \frac{E\left(C_i|A_i, B_i, X_i, D_i, W_i\right)}{E\left(C_i|A_i, X_i\right)} \left\{W_i - \mu(a,0)\right\} I(A_i = a) = 0.$$

Note that this is a mean-zero estimating function provided that $E\left(\epsilon_i|C_i = 1, X_i\right) = 0$. That is, among compliers, the self-reported error is not systemic at all levels of the confounders. As in the main paper, for simplicity we consider only a single-arm trial with $a = 1$ for all participants, but the results easily generalize to multi-arm trials.

$$
\begin{aligned}
& E\left[\frac{E\left(C_i|B_i, X_i, D_i, W_i\right)}{E\left(C_i|X_i\right)}\left\{W_i - \mu(1,0)\right\}\right] \\
& = E\left[\frac{C_i}{E\left(C_i|X_i\right)}\left\{Y_i + \epsilon - \mu(1,0)\right\}\right] \\
& = E\left[\frac{C_i}{E\left(C_i|X_i\right)}\left\{Y_i - \mu(1,0)\right\} + \frac{C_i}{E\left(C_i|X_i\right)}\epsilon_i\right] \\
& = 0 + E\left[\frac{C_i}{E\left(C_i|X_i\right)}E\left(\epsilon_i|C_i, X_i\right)\right] \\
& = E\left[\frac{C_i}{E\left(C_i|X_i\right)}E\left(\epsilon_i|C_i = 1, X_i\right)\right] = 0.
\end{aligned}
$$

Appendix C

Chapter 4 Appendix

C.1 Additional simulation results: no participants with known compliance status

Table C.1: Chapter 4 Simulation Results: No Interaction or Quadratic Coefficient, Outliers Removed, No Known Compliers

	$n = 250$				$n = 500$				$n = 1000$			
Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
IPW	0.008	0.231	0.054	6	0.007	0.160	0.026	1	0.004	0.109	0.012	5
REG	0.003	0.209	0.044	5	0.004	0.147	0.022	2	0.001	0.102	0.010	5
A-IPW	0.002	0.212	0.045	5	0.004	0.147	0.022	2	0.002	0.103	0.011	5
CURE	-0.040	0.356	0.128	15	-0.011	0.234	0.055	5	-0.009	0.153	0.024	5
CURE+	0.010	0.291	0.085	16	0.006	0.204	0.042	3	0.003	0.138	0.019	4
EM-REG	-0.002	0.280	0.078	14	0.002	0.194	0.038	3	0.001	0.136	0.019	2
W-REG	-0.047	0.348	0.123	10	-0.015	0.230	0.053	3	-0.009	0.151	0.023	5
A-CURE	-0.051	0.349	0.124	10	-0.015	0.231	0.054	3	-0.008	0.151	0.023	5

n_O: number of outliers

Table C.2: Chapter 4 Simulation Results: Interaction Model Correctly Specified, Outliers Removed, No Known Compliers

		$n = 250$				$n = 500$				$n = 1000$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.026	0.404	0.164	8	0.010	0.283	0.080	1	0.010	0.183	0.033	4
	REG	0.008	0.354	0.125	5	0.008	0.253	0.064	1	0.005	0.166	0.028	6
	A-IPW	0.008	0.355	0.126	5	0.007	0.253	0.064	1	0.005	0.165	0.027	7
	CURE	-0.039	0.510	0.262	25	-0.014	0.346	0.120	14	-0.006	0.208	0.043	11
	CURE+	0.037	0.449	0.203	11	0.012	0.310	0.097	1	0.010	0.197	0.039	3
	EM-REG	0.003	0.419	0.175	0	0.005	0.284	0.081	2	0.006	0.187	0.035	3
	W-REG	-0.060	0.447	0.204	10	-0.023	0.312	0.098	14	-0.010	0.200	0.040	6
	A-CURE	-0.061	0.450	0.206	12	-0.023	0.313	0.098	14	-0.009	0.201	0.040	6
2	IPW	0.040	0.638	0.409	3	0.014	0.438	0.192	1	0.015	0.280	0.079	5
	REG	0.017	0.540	0.292	4	0.011	0.391	0.153	0	0.009	0.249	0.062	8
	A-IPW	0.016	0.539	0.290	5	0.010	0.391	0.153	0	0.009	0.248	0.061	9
	CURE	-0.031	0.740	0.549	25	-0.013	0.491	0.241	11	-0.002	0.296	0.088	11
	CURE+	0.060	0.662	0.442	10	0.019	0.453	0.206	1	0.016	0.283	0.080	7
	EM-REG	0.013	0.590	0.349	1	0.008	0.411	0.169	1	0.009	0.266	0.071	6
	W-REG	-0.056	0.607	0.371	3	-0.018	0.434	0.188	8	-0.003	0.274	0.075	9
	A-CURE	-0.055	0.608	0.373	5	-0.018	0.434	0.189	8	-0.003	0.275	0.076	8

n_O: number of outliers

Table C.3: Chapter 4 Simulation Results: Quadratic Model Correctly Specified, Outliers Removed, No Known Compliers

		$n = 250$				$n = 500$				$n = 1000$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.010	0.440	0.193	1	0.012	0.290	0.084	4	0.007	0.195	0.038	4
	REG	0.010	0.400	0.160	0	0.008	0.277	0.077	3	0.005	0.185	0.034	6
	A-IPW	0.010	0.400	0.160	0	0.008	0.278	0.077	3	0.005	0.185	0.034	6
	CURE	-0.035	0.552	0.305	27	0.002	0.365	0.133	14	-0.006	0.230	0.053	10
	CURE+	0.014	0.470	0.221	7	0.013	0.325	0.106	5	0.004	0.213	0.046	4
	EM-REG	0.001	0.442	0.196	2	0.006	0.309	0.096	3	0.003	0.205	0.042	5
	W-REG	-0.067	0.482	0.236	7	-0.019	0.334	0.112	7	-0.012	0.219	0.048	11
	A-CURE	-0.067	0.481	0.236	11	-0.017	0.333	0.111	8	-0.012	0.219	0.048	11
2	IPW	0.018	0.709	0.503	1	0.013	0.475	0.226	3	0.009	0.315	0.099	4
	REG	0.018	0.646	0.418	0	0.011	0.454	0.206	3	0.007	0.303	0.092	4
	A-IPW	0.018	0.647	0.418	0	0.011	0.454	0.206	3	0.008	0.303	0.092	4
	CURE	-0.030	0.837	0.702	22	0.011	0.550	0.302	10	-0.000	0.344	0.119	4
	CURE+	0.029	0.734	0.539	3	0.017	0.506	0.256	7	0.008	0.327	0.107	4
	EM-REG	0.016	0.675	0.456	1	0.011	0.477	0.228	5	0.006	0.316	0.100	4
	W-REG	-0.063	0.690	0.480	6	-0.013	0.491	0.242	3	-0.007	0.326	0.106	3
	A-CURE	-0.062	0.689	0.479	6	-0.013	0.491	0.242	3	-0.007	0.326	0.106	3

n_O: number of outliers

Table C.4: Chapter 4 Simulation Results: Misspecified Interaction Model, Outliers Removed, No Known Compliers

		$n = 250$				$n = 500$				$n = 1000$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.026	0.404	0.164	8	0.010	0.283	0.080	1	0.010	0.183	0.033	4
	REG	-0.035	0.382	0.147	4	-0.037	0.275	0.077	0	-0.037	0.178	0.033	5
	A-IPW	0.000	0.396	0.157	3	0.000	0.280	0.079	0	0.004	0.182	0.033	6
	CURE	-0.039	0.510	0.262	25	-0.014	0.346	0.120	14	-0.006	0.208	0.043	11
	CURE+	0.150	0.549	0.324	29	0.182	0.363	0.165	8	0.192	0.230	0.090	3
	EM-REG	-0.027	0.515	0.266	30	0.027	0.348	0.122	6	0.043	0.219	0.050	5
	W-REG	-0.096	0.487	0.247	14	-0.065	0.348	0.126	14	-0.048	0.220	0.051	9
	A-CURE	-0.042	0.501	0.253	22	-0.020	0.354	0.126	14	-0.005	0.224	0.050	8
2	IPW	0.040	0.638	0.409	3	0.014	0.438	0.192	1	0.015	0.280	0.079	5
	REG	-0.075	0.611	0.378	5	-0.079	0.442	0.201	0	-0.076	0.286	0.088	3
	A-IPW	-0.002	0.643	0.414	2	-0.005	0.452	0.204	1	0.005	0.294	0.087	4
	CURE	-0.031	0.740	0.549	25	-0.013	0.491	0.241	11	-0.002	0.296	0.088	11
	CURE+	-0.747	2.366	6.158	148	-0.601	1.417	2.369	142	-0.863	1.096	1.946	96
	EM-REG	-0.578	3.078	9.811	86	-1.330	1.437	3.833	133	-1.365	1.021	2.904	61
	W-REG	-0.142	0.734	0.558	11	-0.111	0.522	0.285	10	-0.083	0.330	0.116	12
	A-CURE	-0.041	0.757	0.575	22	-0.025	0.534	0.286	12	0.001	0.339	0.115	10

n_O: number of outliers

Table C.5: Chapter 4 Simulation Results: Misspecified Quadratic Model, Outliers Removed, No Known Compliers

		$n = 250$				$n = 500$				$n = 1000$			
Coef.	Estimator	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O	Bias	MCSD	MSE	n_O
1	IPW	0.010	0.440	0.193	1	0.012	0.290	0.084	4	0.007	0.195	0.038	4
	REG	-0.128	0.445	0.214	0	-0.113	0.313	0.111	3	-0.115	0.214	0.059	3
	A-IPW	-0.017	0.462	0.214	0	-0.005	0.326	0.106	7	-0.003	0.220	0.048	5
	CURE	-0.035	0.552	0.305	27	0.002	0.365	0.133	14	-0.006	0.230	0.053	10
	CURE+	0.381	0.534	0.430	57	0.408	0.366	0.300	37	0.399	0.255	0.224	9
	EM-REG	0.199	0.506	0.296	67	0.211	0.352	0.168	39	0.205	0.244	0.102	9
	W-REG	-0.223	0.580	0.386	10	-0.154	0.401	0.185	11	-0.131	0.267	0.089	12
	A-CURE	-0.079	0.592	0.356	26	-0.024	0.418	0.175	14	-0.011	0.270	0.073	11
2	IPW	0.018	0.709	0.503	1	0.013	0.475	0.226	3	0.009	0.315	0.099	4
	REG	-0.259	0.764	0.651	0	-0.231	0.546	0.352	2	-0.231	0.369	0.189	2
	A-IPW	-0.038	0.799	0.639	1	-0.012	0.577	0.333	5	-0.012	0.385	0.149	2
	CURE	-0.030	0.837	0.702	22	0.011	0.550	0.302	10	-0.000	0.344	0.119	4
	CURE+	-1.325	8.085	67.132	74	-2.147	7.382	59.105	49	-2.773	7.033	57.151	80
	EM-REG	6.641	6.444	85.628	5	6.263	5.776	72.593	5	6.632	4.782	66.841	2
	W-REG	-0.410	0.943	1.058	11	-0.298	0.664	0.530	6	-0.249	0.441	0.256	4
	A-CURE	-0.124	0.993	1.002	19	-0.036	0.703	0.496	11	-0.012	0.448	0.201	5

n_O: number of outliers

C.2 Additional Application Tables

Table C.6: Estimated mixture distribution coefficients and parameters

	CURE Estimator		CURE+ Estimator	
Parameter	$C = 1$	$C = 0$	$C = 1$	$C = 0$
$\hat{\gamma_0}$	0.12(-0.79, 0.87)	3.33(2.80, 3.97)	0.06(-0.81, 0.96)	3.37(2.73, 3.95)
$\hat{\gamma_1}$	0.02(-0.00, 0.07)	0.01(-0.03, 0.04)	0.04(0.00, 0.07)	0.01(-0.02, 0.05)
$\hat{\sigma}$	0.89(0.60, 1.14)	0.78(0.58, 0.97)	1.12(0.59, 1.39)	0.76(0.55, 1.07)

Estimated mixture distribution coefficients and parameters (95% bootstrap percentile intervals) assuming $B|Y, C, D = 1 \sim N(\gamma_0 + \gamma_1 Y, \sigma^2)$. $B = \log(TNE)$, $Y =$ study cigarettes smoked per day. $C = 1$ indicates the component density for compliers, $C = 0$ indicates the component density for non-compliers.

Table C.7: Estimated coefficients for the logistic model $\Pr(C = 1|X, Y)$ (CURE Estimator) and $\Pr(C = 1|X)$ (CURE+ estimator)

Coefficient	CURE Estimator	CURE+ Estimator
Intercept	1.26(-1.92, 6.12)	1.15(-1.92, 6.22)
Age	0.02(-0.03, 0.07)	0.02(-0.02, 0.06)
Baseline log(TNE)	-0.94(-2.08, -0.46)	-0.94(-2.14, -0.42)
Baseline Cigarettes per day	-0.01(-0.17, 0.14)	0.03(-0.12, 0.10)
Max Symptoms Week 1	0.03(-0.07, 0.12)	0.03(-0.07, 0.12)
MNWS Week 5	0.09(-0.05, 0.25)	0.11(-0.05, 0.27)
QSU Study Cigarettes Week 5	0.05(-0.02, 0.15)	0.07(-0.02, 0.17)
QSU Usual Brand Cigarettes Week 5	-0.05(-0.14, -0.01)	-0.06(-0.15, -0.00)
CES Satisfaction Week 5	0.20(-0.29, 0.68)	0.10(-0.35, 0.69)
Y (Study Cigarettes per day)	-0.00(-0.15, 0.11)	–

Estimated coefficients (95% bootstrap percentile intervals) for the logistic model $\Pr(C = 1|X, Y)$ (CURE Estimator) and $\Pr(C = 1|X)$ (CURE+ estimator) estimated as part of the mixture density (i.e., estimated for the numerator of the weights).

Table C.8: Estimated coefficients and parameters for the linear model for $Y|X, C$

	CURE+ Estimator		W-REG Estimator
Coefficient	$C = 1$	$C = 0$	$C = 1$
Intercept	-11.57(-23.99, 0.51)	-0.57(-15.36, 7.51)	-10.60(-24.59, 2.13)
Age	0.08(-0.07, 0.33)	0.09(0.00, 0.21)	0.11(-0.09, 0.34)
Baseline log(TNE)	-0.16(-4.52, 2.74)	-0.55(-2.38, 0.87)	-0.59(-5.00, 2.88)
Baseline Cigarettes per day	1.58(0.48, 2.08)	0.86(0.75, 1.54)	1.41(0.59, 2.09)
Max Symptoms Week 1	-0.01(-0.57, 0.32)	-0.09(-0.27, 0.23)	-0.10(-0.54, 0.33)
MNWS Week 5	-0.29(-0.86, 0.43)	-0.27(-0.61, 0.30)	-0.27(-0.89, 0.38)
QSU Study Cigarettes Week 5	0.01(-0.37, 0.43)	-0.06(-0.20, 0.17)	-0.06(-0.38, 0.36)
QSU Usual Brand Cigarettes Week 5	0.01(-0.30, 0.38)	0.09(-0.09, 0.18)	0.07(-0.29, 0.39)
CES Satisfaction Week 5	1.26(-0.67, 4.19)	0.52(-0.45, 1.71)	1.69(-0.82, 3.87)

Estimated coefficients and parameters (95% bootstrap percentile intervals) for the linear model for $Y|X, C$ estimated as part of the mixture distribution (CURE+ estimator) or using weights $\hat{E}(C|B, X, Y)$ (W-REG estimator). $C = 1$ indicates the component density for compliers, $C = 0$ indicates the component density for non-compliers. $C = 0$ is missing for the W-REG estimator because the estimator only requires coefficients for $C = 1$.

Table C.9: Estimated coefficients for the logistic model $\Pr(C = 1|X)$

Coefficient	CURE Estimator	CURE+ Estimator
Intercept	-0.71(-3.72, 4.64)	-0.89(-4.05, 4.64)
Age	0.02(-0.03, 0.08)	0.02(-0.03, 0.08)
Baseline log(TNE)	-0.47(-1.63, 0.03)	-0.39(-1.63, 0.05)
Baseline Cigarettes per day	-0.06(-0.17, 0.02)	-0.03(-0.18, 0.04)
Max Symptoms Week 1	0.01(-0.08, 0.12)	0.01(-0.08, 0.12)
MNWS Week 5	0.05(-0.10, 0.22)	0.05(-0.10, 0.22)
QSU Study Cigarettes Week 5	0.01(-0.06, 0.12)	0.02(-0.06, 0.12)
QSU Usual Brand Cigarettes Week 5	-0.03(-0.13, 0.01)	-0.04(-0.13, 0.01)
CES Satisfaction Week 5	0.42(-0.13, 1.00)	0.36(-0.17, 1.04)

Estimated coefficients (95% bootstrap percentile intervals) for the logistic model $\Pr(C = 1|X)$, the denominator of the weights